

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 15:42:43 ON 04 NOV 2003

=> fil .bec

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.48

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,  
ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 15:43:20 ON 04 NOV 2003  
ALL COPYRIGHTS AND RESTRICTIONS APPLY. SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s ikk?

FILE 'MEDLINE'

L1 1793 IKK?

FILE 'SCISEARCH'

L2 958 IKK?

FILE 'LIFESCI'

L3 384 IKK?

FILE 'BIOTECHDS'

L4 41 IKK?

FILE 'BIOSIS'

L5 887 IKK?

FILE 'EMBASE'

L6 621 IKK?

FILE 'HCAPLUS'

L7 923 IKK?

FILE 'NTIS'

L8 37 IKK?

FILE 'ESBIOBASE'

L9 564 IKK?

FILE 'BIOTECHNO'

L10 432 IKK?

FILE 'WPIDS'

L11 89 IKK?

TOTAL FOR ALL FILES

L12 6729 IKK?

=> s l12(5a)bind?

FILE 'MEDLINE'

678554 BIND?

L13 59 L1 (5A)BIND?

FILE 'SCISEARCH'

635497 BIND?

L14 64 L2 (5A)BIND?

FILE 'LIFESCI'

230121 BIND?

L15 37 L3 (5A)BIND?

FILE 'BIOTECHDS'  
36180 BIND?  
L16 10 L4 (5A) BIND?

FILE 'BIOSIS'  
630371 BIND?  
L17 77 L5 (5A) BIND?

FILE 'EMBASE'  
589419 BIND?  
L18 48 L6 (5A) BIND?

FILE 'HCAPLUS'  
1008027 BIND?  
L19 73 L7 (5A) BIND?

FILE 'NTIS'  
14666 BIND?  
L20 0 L8 (5A) BIND?

FILE 'ESBIOBASE'  
223365 BIND?  
L21 48 L9 (5A) BIND?

FILE 'BIOTECHNO'  
287237 BIND?  
L22 36 L10 (5A) BIND?

FILE 'WPIDS'  
250596 BIND?  
L23 17 L11 (5A) BIND?

TOTAL FOR ALL FILES  
L24 469 L12 (5A) BIND?

=> s spa-1  
FILE 'MEDLINE'  
3334 SPA  
3094748 1  
L25 40 SPA-1  
(SPA(W) 1)

FILE 'SCISEARCH'  
2534 SPA  
3174460 1  
L26 34 SPA-1  
(SPA(W) 1)

FILE 'LIFESCI'  
731 "SPA"  
525713 "1"  
L27 17 SPA-1  
("SPA" (W) "1")

FILE 'BIOTECHDS'  
148 SPA  
163253 1  
L28 4 SPA-1  
(SPA(W) 1)

FILE 'BIOSIS'  
2698 SPA  
2988174 1

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L29          40 SPA-1
              (SPA(W) 1)

FILE 'EMBASE'
      3421 "SPA"
      1893841 "1"
L30          34 SPA-1
              ("SPA" (W) "1")

FILE 'HCAPLUS'
      2793 SPA
      7717384 1
L31          46 SPA-1
              (SPA(W) 1)

FILE 'NTIS'
      233 SPA
      503879 1
L32          6 SPA-1
              (SPA(W) 1)

FILE 'ESBIOBASE'
      827 SPA
      881440 1
L33          23 SPA-1
              (SPA(W) 1)

FILE 'BIOTECHNO'
      804 SPA
      659640 1
L34          18 SPA-1
              (SPA(W) 1)

FILE 'WPIDS'
      1221 SPA
      6989961 1
L35          9 SPA-1
              (SPA(W) 1)

TOTAL FOR ALL FILES
L36          271 SPA-1

=> s l36 and bind?
FILE 'MEDLINE'
      678554 BIND?
L37          19 L25 AND BIND?

FILE 'SCISEARCH'
      635497 BIND?
L38          12 L26 AND BIND?

FILE 'LIFESCI'
      230121 BIND?
L39          5 L27 AND BIND?

FILE 'BIOTECHDS'
      36180 BIND?
L40          2 L28 AND BIND?

FILE 'BIOSIS'
      630371 BIND?
L41          8 L29 AND BIND?

FILE 'EMBASE'

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      589419 BIND?
L42      10 L30 AND BIND?

FILE 'HCAPLUS'
      1008027 BIND?
L43      22 L31 AND BIND?

FILE 'NTIS'
      14666 BIND?
L44      0 L32 AND BIND?

FILE 'ESBIOBASE'
      223365 BIND?
L45      3 L33 AND BIND?

FILE 'BIOTECHNO'
      287237 BIND?
L46      8 L34 AND BIND?

FILE 'WPIDS'
      250596 BIND?
L47      2 L35 AND BIND?

TOTAL FOR ALL FILES
L48      91 L36 AND BIND?

=> s l12 and l36
FILE 'MEDLINE'
L49      0 L1 AND L25

FILE 'SCISEARCH'
L50      0 L2 AND L26

FILE 'LIFESCI'
L51      0 L3 AND L27

FILE 'BIOTECHDS'
L52      1 L4 AND L28

FILE 'BIOSIS'
L53      0 L5 AND L29

FILE 'EMBASE'
L54      0 L6 AND L30

FILE 'HCAPLUS'
L55      0 L7 AND L31

FILE 'NTIS'
L56      0 L8 AND L32

FILE 'ESBIOBASE'
L57      0 L9 AND L33

FILE 'BIOTECHNO'
L58      0 L10 AND L34

FILE 'WPIDS'
L59      1 L11 AND L35

TOTAL FOR ALL FILES
L60      2 L12 AND L36

=> s (l24 or l48 or l60)

```

FILE 'MEDLINE'  
L61 78 (L13 OR L37 OR L49)

FILE 'SCISEARCH'  
L62 76 (L14 OR L38 OR L50)

FILE 'LIFESCI'  
L63 42 (L15 OR L39 OR L51)

FILE 'BIOTECHDS'  
L64 12 (L16 OR L40 OR L52)

FILE 'BIOSIS'  
L65 85 (L17 OR L41 OR L53)

FILE 'EMBASE'  
L66 58 (L18 OR L42 OR L54)

FILE 'HCAPLUS'  
L67 95 (L19 OR L43 OR L55)

FILE 'NTIS'  
L68 0 (L20 OR L44 OR L56)

FILE 'ESBIOBASE'  
L69 51 (L21 OR L45 OR L57)

FILE 'BIOTECHNO'  
L70 44 (L22 OR L46 OR L58)

FILE 'WPIDS'  
L71 19 (L23 OR L47 OR L59)

TOTAL FOR ALL FILES  
L72 560 (L24 OR L48 OR L60)

=> s l72 not 2002-2003/py

FILE 'MEDLINE'  
969436 2002-2003/PY  
L73 47 L61 NOT 2002-2003/PY

FILE 'SCISEARCH'  
1784572 2002-2003/PY  
L74 48 L62 NOT 2002-2003/PY

FILE 'LIFESCI'  
150213 2002-2003/PY  
L75 28 L63 NOT 2002-2003/PY

FILE 'BIOTECHDS'  
38640 2002-2003/PY  
L76 5 L64 NOT 2002-2003/PY

FILE 'BIOSIS'  
886937 2002-2003/PY  
L77 53 L65 NOT 2002-2003/PY

FILE 'EMBASE'  
798001 2002-2003/PY  
L78 32 L66 NOT 2002-2003/PY

FILE 'HCAPLUS'  
1890883 2002-2003/PY  
L79 55 L67 NOT 2002-2003/PY

FILE 'NTIS'  
19764 2002-2003/PY  
L80 0 L68 NOT 2002-2003/PY

FILE 'ESBIOBASE'  
510234 2002-2003/PY  
L81 29 L69 NOT 2002-2003/PY

FILE 'BIOTECHNO'  
221769 2002-2003/PY  
L82 26 L70 NOT 2002-2003/PY

FILE 'WPIDS'  
1872499 2002-2003/PY  
L83 5 L71 NOT 2002-2003/PY

TOTAL FOR ALL FILES  
L84 328 L72 NOT 2002-2003/PY

=> s l24 and (ldhm or eif3? or slap2 or kiaa0614 or sart-1 or gbrd1 or i-traf or  
numa1 or pn13730)

FILE 'MEDLINE'  
2 LDHM  
151 EIF3?  
1 SLAP2  
0 KIAA0614  
144 SART  
3094748 1  
21 SART-1  
(SART(W)1)  
0 GBRD1  
1056511 I  
363 TRAF  
6 I-TRAF  
(I(W)TRAF)  
0 NUMA1  
0 PN13730  
L85 0 L13 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1  
OR I-TRAF OR NUMA1 OR PN13730)

FILE 'SCISEARCH'  
0 LDHM  
156 EIF3?  
1 SLAP2  
0 KIAA0614  
162 SART  
3174460 1  
10 SART-1  
(SART(W)1)  
0 GBRD1  
973696 I  
424 TRAF  
5 I-TRAF  
(I(W)TRAF)  
0 NUMA1  
0 PN13730  
L86 0 L14 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1  
OR I-TRAF OR NUMA1 OR PN13730)

FILE 'LIFESCI'  
0 LDHM  
101 EIF3?  
1 SLAP2

```

0 KIAA0614
35 "SART"
525713 "1"
3 SART-1
("SART" (W) "1")
0 GBRD1
246140 "I"
232 "TRAF"
3 I-TRAF
("I" (W) "TRAF")
0 NUMA1
0 PN13730
L87 0 L15 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
OR I-TRAF OR NUMA1 OR PN13730)

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FILE 'BIOTECHDS'

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1 LDHM
7 EIF3?
2 SLAP2
1 KIAA0614
8 SART
163253 1
5 SART-1
(SART(W) 1)
0 GBRD1
69292 I
32 TRAF
2 I-TRAF
(I (W) TRAF)
1 NUMA1
1 PN13730
L88 0 L16 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
OR I-TRAF OR NUMA1 OR PN13730)

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FILE 'BIOSIS'

```

3 LDHM
170 EIF3?
2 SLAP2
0 KIAA0614
206 SART
2988174 1
18 SART-1
(SART(W) 1)
0 GBRD1
831068 I
463 TRAF
8 I-TRAF
(I (W) TRAF)
0 NUMA1
0 PN13730
L89 0 L17 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
OR I-TRAF OR NUMA1 OR PN13730)

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FILE 'EMBASE'

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1 LDHM
116 EIF3?
1 SLAP2
0 KIAA0614
128 "SART"
1893841 "1"
8 SART-1
("SART" (W) "1")
0 GBRD1
750454 "I"

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323 "TRAF"
5 I-TRAF
  ("I" (W) "TRAF")
0 NUMA1
0 PN13730
L90 0 L18 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
    OR I-TRAF OR NUMA1 OR PN13730)

FILE 'HCAPLUS'
5 LDHM
215 EIF3?
9 SLAP2
2 KIAA0614
125 SART
7717384 1
27 SART-1
  (SART(W) 1)
0 GBRD1
3913649 I
539 TRAF
13 I-TRAF
  (I (W) TRAF)
9 NUMA1
1 PN13730
L91 0 L19 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
    OR I-TRAF OR NUMA1 OR PN13730)

FILE 'NTIS'
0 LDHM
1 EIF3?
0 SLAP2
0 KIAA0614
11 SART
503879 1
0 SART-1
  (SART(W) 1)
0 GBRD1
123527 I
29 TRAF
0 I-TRAF
  (I (W) TRAF)
0 NUMA1
0 PN13730
L92 0 L20 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
    OR I-TRAF OR NUMA1 OR PN13730)

FILE 'ESBIOBASE'
0 LDHM
111 EIF3?
1 SLAP2
0 KIAA0614
29 SART
881440 1
7 SART-1
  (SART(W) 1)
0 GBRD1
263846 I
299 TRAF
4 I-TRAF
  (I (W) TRAF)
0 NUMA1
0 PN13730
L93 0 L21 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
    OR I-TRAF OR NUMA1 OR PN13730)

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FILE 'BIOTECHNO'
    0 LDHM
    102 EIF3?
    1 SLAP2
    0 KIAA0614
    32 SART
659640 1
    8 SART-1
        (SART(W)1)
    0 GBRD1
213683 I
    254 TRAF
    4 I-TRAF
        (I(W)TRAF)
    0 NUMA1
    0 PN13730
L94    0 L22 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
        OR I-TRAF OR NUMA1 OR PN13730)

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FILE 'WPIDS'
    2 LDHM
    10 EIF3?
    2 SLAP2
    1 KIAA0614
    28 SART
6989961 1
    6 SART-1
        (SART(W)1)
    0 GBRD1
1142808 I
    44 TRAF
    5 I-TRAF
        (I(W)TRAF)
    1 NUMA1
    1 PN13730
L95    0 L23 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
        OR I-TRAF OR NUMA1 OR PN13730)

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TOTAL FOR ALL FILES

```

L96    0 L24 AND (LDHM OR EIF3? OR SLAP2 OR KIAA0614 OR SART-1 OR GBRD1
        OR I-TRAF OR NUMA1 OR PN13730)

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=> dup rem 172

PROCESSING COMPLETED FOR L72

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L97    150 DUP REM L72 (410 DUPLICATES REMOVED)

```

=> d tot

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L97    ANSWER 1 OF 150  BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
TI     Reducing mammary epithelial cell proliferation, useful for treating
        breast cancer, comprises administering an agent that specifically reduces
        IKK alpha kinase activity to the mammary epithelial cells;
        cell proliferation reduction and recombinant enzyme protein for use in
        disease therapy
AU     CAO Y; KARIN M
AN     2003-17453  BIOTECHDS
PI     WO 2003043568 30 May 2003

```

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L97    ANSWER 2 OF 150  WPIDS  COPYRIGHT 2003 THOMSON DERWENT on STN
TI     New tricyclic compounds are I-kappa B kinase inhibitors used for treating
        e.g. inflammation and cancer.
PI     WO 2003070706 A1 20030828 (200368)* EN    61p    C07D231-54
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS

```

LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
 ZM ZW  
 IN CLARE, M; LENNON, P; METZ, S; VAZQUEZ, M; WEIER, R M; WOLFSON, S G; XU, X

L97 ANSWER 3 OF 150 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
 TI New **SPA-1**, SPA-2, SPA-3, SHB-PA104, SHB-PA105 and  
 SHB-PA106 polypeptides and polynucleotides from *Pseudomonas aeruginosa*,  
 useful for treating or preventing pneumonia, bacteremia, chronic infection  
 or septicemia.  
 PI WO 2003042240 A2 20030522 (200342)\* EN 32p C07K014-21  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU  
 MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU  
 ZA ZM ZW  
 IN BRODEUR, B R; BUSSIÈRE, D; CHARLAND, N; CHARLEBOIS, I; HAMEL, J; MARTIN, D

L97 ANSWER 4 OF 150 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
 TI Use of Ikb kinase-beta inhibitor in reducing or preventing ischemic  
 reperfusion injury.  
 PI WO 2003041640 A2 20030522 (200344)\* EN 19p A61K000-00  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU  
 MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
 ZM ZW  
 US 2003118578 A1 20030626 (200349) A61K048-00  
 IN AHN, Y; ROSENZWEIG, A

L97 ANSWER 5 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 2  
 TI Oncoprotein suppression of tumor necrosis factor-induced NF kappa B  
 activation is independent of Raf-controlled pathways  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (12 SEP 2003) Vol. 278, No. 37, pp.  
 34910-34917.  
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE  
 PIKE, BETHESDA, MD 20814-3996 USA.  
 ISSN: 0021-9258.  
 AU Hanson J L; Anest V; Reuther-Madrid J; Baldwin A S (Reprint)  
 AN 2003:782901 SCISEARCH

L97 ANSWER 6 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI IKKi/IKKε Plays a Key Role in Integrating Signals Induced by  
 Pro-inflammatory Stimuli  
 SO Journal of Biological Chemistry (2003), 278(29), 26612-26619  
 CODEN: JBCHA3; ISSN: 0021-9258  
 AU Kravchenko, Vladimir V.; Mathison, John C.; Schwamborn, Klaus; Mercurio,  
 Frank; Ulevitch, Richard J.  
 AN 2003:536925 HCAPLUS  
 DN 139:163470

L97 ANSWER 7 OF 150 MEDLINE on STN DUPLICATE 3  
 TI AF-6 controls integrin-mediated cell adhesion by regulating Rap1  
 activation through the specific recruitment of Rap1GTP and **SPA-1**.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Apr 25) 278 (17) 15232-8.  
 Journal code: 2985121R. ISSN: 0021-9258.

AU Su Li; Hattori Masakazu; Moriyama Masaki; Murata Norihito; Harazaki Masashi; Kaibuchi Kozo; Minato Nagahiro  
AN 2003198289 MEDLINE

L97 ANSWER 8 OF 150 MEDLINE on STN DUPLICATE 4  
TI Antigen-driven T cell anergy and defective memory T cell response via deregulated Rap1 activation in **SPA-1**-deficient mice.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2003 Sep 16) 100 (19) 10919-24.  
Journal code: 7505876. ISSN: 0027-8424.  
AU Ishida Daisuke; Yang Hailin; Masuda Kyoko; Uesugi Kanami; Kawamoto Hiroshi; Hattori Masakazu; Minato Nagahiro  
AN 2003435807 MEDLINE

L97 ANSWER 9 OF 150 MEDLINE on STN DUPLICATE 5  
TI Protection of islets by in situ peptide-mediated transduction of the Ikappa B kinase inhibitor Nemo-binding domain peptide.  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Mar 14) 278 (11) 9862-8.  
Journal code: 2985121R. ISSN: 0021-9258.  
AU Rehman Khaja K; Bertera Suzanne; Bottino Rita; Balamurugan A N; Mai Jeffrey C; Mi Zhibao; Trucco Massimo; Robbins Paul D  
AN 2003113510 MEDLINE

L97 ANSWER 10 OF 150 MEDLINE on STN DUPLICATE 6  
TI KSHV vFLIP **binds** to **IKK**-gamma to activate **IKK**.  
SO JOURNAL OF CELL SCIENCE, (2003 Sep 15) 116 (Pt 18) 3721-8.  
Journal code: 0052457. ISSN: 0021-9533.  
AU Field Nigel; Low Walter; Daniels Mark; Howell Steven; Daviet Laurent; Boshoff Chris; Collins Mary  
AN 2003468947 IN-PROCESS

L97 ANSWER 11 OF 150 MEDLINE on STN DUPLICATE 7  
TI An affibody in complex with a target protein: structure and coupled folding.  
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2003 Mar 18) 100 (6) 3185-90.  
Journal code: 7505876. ISSN: 0027-8424.  
AU Wahlberg Elisabet; Lendel Christofer; Helgstrand Magnus; Allard Peter; Dincbas-Renqvist Vildan; Hedqvist Anders; Berglund Helena; Nygren Per-Ake; Hard Torleif  
AN 2003130524 MEDLINE

L97 ANSWER 12 OF 150 MEDLINE on STN DUPLICATE 8  
TI Caspase-8 and caspase-10 activate NF-kappaB through RIP, NIK and IKKalpha kinases.  
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (2003 Jul) 33 (7) 1998-2006.  
Journal code: 1273201. ISSN: 0014-2980.  
AU Shikama Yoshiaki; Yamada Masao; Miyashita Toshiyuki  
AN 2003352190 MEDLINE

L97 ANSWER 13 OF 150 MEDLINE on STN DUPLICATE 9  
TI Human T-lymphotropic virus type I tax activates I-kappa B kinase by inhibiting I-kappa B kinase-associated serine/threonine protein phosphatase 2A.  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Jan 17) 278 (3) 1487-93.  
Journal code: 2985121R. ISSN: 0021-9258.  
AU Fu De-Xue; Kuo Yu-Liang; Liu Bao-Ying; Jeang Kuan-Teh; Giam Chou-Zen  
AN 2003032305 MEDLINE

L97 ANSWER 14 OF 150 MEDLINE on STN DUPLICATE 10  
TI BMS-345541 is a highly selective inhibitor of I kappa B kinase that binds at an allosteric site of the enzyme and blocks NF-kappa B-dependent transcription in mice.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2003 Jan 17) 278 (3) 1450-6.  
Journal code: 2985121R. ISSN: 0021-9258.

AU Burke James R; Pattoli Mark A; Gregor Kurt R; Brassil Patrick J; MacMaster John F; McIntyre Kim W; Yang Xiaoxia; Iotzova Violetta S; Clarke Wendy; Strnad Joann; Qiu Yuping; Zusi F Christopher

AN 2003032299 MEDLINE

L97 ANSWER 15 OF 150 MEDLINE on STN DUPLICATE 11

TI Triggering the interferon antiviral response through an IKK-related pathway.

SO SCIENCE, (2003 May 16) 300 (5622) 1148-51.  
Journal code: 0404511. ISSN: 1095-9203.

AU Sharma Sonia; tenOever Benjamin R; Grandvaux Nathalie; Zhou Guo-Ping; Lin Rongtuan; Hiscott John

AN 2003228927 MEDLINE

L97 ANSWER 16 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Triggering the interferon antiviral response through an IKK-related pathway

SO SCIENCE, (16 MAY 2003) Vol. 300, No. 5622, pp. 1148-1151.  
Publisher: AMER ASSOC ADVANCEMENT SCIENCE, 1200 NEW YORK AVE, NW, WASHINGTON, DC 20005 USA.  
ISSN: 0036-8075.

AU Sharma S; tenOever B R; Grandvaux N; Zhou G P; Lin R T (Reprint); Hiscott J

AN 2003:395225 SCISEARCH

L97 ANSWER 17 OF 150 MEDLINE on STN DUPLICATE 12

TI Inhibition of IkappaB kinase by a new class of retinoid-related anticancer agents that induce apoptosis.

SO MOLECULAR AND CELLULAR BIOLOGY, (2003 Feb) 23 (3) 1061-74.  
Journal code: 8109087. ISSN: 0270-7306.

AU Bayon Yolanda; Ortiz Maria A; Lopez-Hernandez Francisco J; Gao Feng; Karin Michael; Pfahl Magnus; Piedrafita F Javier

AN 2003022973 MEDLINE

L97 ANSWER 18 OF 150 MEDLINE on STN DUPLICATE 13

TI Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis.

SO BLOOD, (2003 Feb 1) 101 (3) 1053-62.  
Journal code: 7603509. ISSN: 0006-4971.

AU Bharti Alok C; Donato Nicholas; Singh Sujay; Aggarwal Bharat B

AN 2003022721 MEDLINE

L97 ANSWER 19 OF 150 MEDLINE on STN DUPLICATE 14

TI Histone H3 phosphorylation by IKK-alpha is critical for cytokine-induced gene expression.

SO NATURE, (2003 Jun 5) 423 (6940) 655-9.  
Journal code: 0410462. ISSN: 0028-0836.

AU Yamamoto Yumi; Verma Udit N; Prajapati Shashi; Kwak Youn-Tae; Gaynor Richard B

AN 2003262820 MEDLINE

L97 ANSWER 20 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Development of Displacement **Binding** and GTPyS Scintillation Proximity Assays for the Identification of Antagonists of the  $\mu$ -Opioid Receptor

SO Assay and Drug Development Technologies (2003), 1(5), 627-636  
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L97 ANSWER 23 OF 150 MEDLINE on STN DUPLICATE 16  
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useful for the diagnosis and treatment of disorders involved in the  
protein-protein interaction, such as rheumatoid arthritis, diabetes,  
asthma, or cancer;  
recombinant protein production and sense and antisense sequence use in  
disease therapy and gene therapy  
AU CIMBORA D M; HEICHMAN K; BARTEL P L  
AN 2003-02219 BIOTECHDS  
PI WO 2002064736 22 Aug 2002

L97 ANSWER 29 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
TI Novel antiinflammatory peptide compounds comprising NEMO binding domain,  
useful for modulating NF-kappaB induction in a cell and for treating  
NF-kappaB-mediated inflammation disorders e.g., asthma, psoriasis,  
vasculitis;  
vector plasmid expression in COS cell and transgenic animal for  
disease therapy  
AU MAY M J; GHOSH S  
AN 2003-10052 BIOTECHDS  
PI US 2002156000 24 Oct 2002

L97 ANSWER 30 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
TI New isolated IKK polypeptide involved in transcription factor activation,  
useful for diagnosing and treating disorders with aberrant activity of  
the IKK polypeptide, such as signal transduction disorders and genetic  
defects;  
involving vector-mediated gene transfer and expression in host cell  
for use in signal transduction disorder and autoimmune disease  
diagnosis and therapy  
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AN 2003-12914 BIOTECHDS  
PI US 6479266 12 Nov 2002

L97 ANSWER 31 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
TI Polynucleotide encoding an I kappa B kinase binding protein Y2H14 and the  
recombinant protein encoded for elucidating and controlling pathways  
leading to inflammation and apoptosis;  
using plasmid pGTB9c and plasmid pBNN132 together with an antibody  
AU MARCU K B  
AN 2002-17097 BIOTECHDS  
PI US 6365722 2 Apr 2002

L97 ANSWER 32 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
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a kinase domain, no leucine zipper like alpha-helix domain, and no  
helix-loop-helix domain, useful for treating inflammation or immune  
diseases, e.g. AIDS;  
vector-mediated protein-kinase gene transfer and expression in host  
cell for recombinant protein production and gene therapy  
AU MARCU K B; CONNELLY M A  
AN 2003-14857 BIOTECHDS  
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ml. e-file.  
CODEN: OGUPE7. ISSN: 0098-1133.  
AU Shoelson, Steven [Inventor]  
AN 2002:622050 BIOSIS

L97 ANSWER 34 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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SO U.S., 73 pp.

CODEN: USXXAM

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DN 137:197335

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TI Characterization of the Ikappa B-kinase NEMO binding domain.  
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B-mediated Inflammatory Response Program  
SO Journal of Biological Chemistry (2002), 277(47), 45129-45140  
CODEN: JBCHA3; ISSN: 0021-9258  
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Patrick; Savitt, Ann; Mische, Sheenah; Li, Jun; Marcu, Kenneth B.  
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L97 ANSWER 37 OF 150 MEDLINE on STN DUPLICATE 25  
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not ligand-induced beta 1 integrin-dependent leukocyte adhesion.  
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Oct 25) 277 (43) 40893-900.  
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John M  
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Keith; Siebenlist Ulrich  
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L97 ANSWER 39 OF 150 MEDLINE on STN DUPLICATE 27  
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L97 ANSWER 40 OF 150 MEDLINE on STN DUPLICATE 28  
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Israel Alain; Veron Michel  
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L97 ANSWER 41 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI Kinetic mechanisms of I $\kappa$ B-related kinases (IKK) inducible IKK and  
 TBK-1 differ from IKK-1/IKK-2 heterodimer  
 SO Journal of Biological Chemistry (2002), 277(15), 12550-12558  
 CODEN: JBCHA3; ISSN: 0021-9258  
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 Tripp, Catherine S.  
 AN 2002:289984 HCAPLUS  
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L97 ANSWER 42 OF 150 MEDLINE on STN DUPLICATE 29  
 TI The zinc finger domain of NEMO is selectively required for NF-kappa B  
 activation by UV radiation and topoisomerase inhibitors.  
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L97 ANSWER 43 OF 150 MEDLINE on STN DUPLICATE 30  
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 interactions and modulates T-cell responses.  
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 receptor-PSD-95 complex in the hippocampus.  
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L97 ANSWER 45 OF 150 MEDLINE on STN DUPLICATE 32  
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 virus oncoprotein Tax.  
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 AN 2002675175 MEDLINE

L97 ANSWER 46 OF 150 MEDLINE on STN DUPLICATE 33  
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 libraries.  
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L97 ANSWER 47 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN  
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 NY 10158-0012 USA.  
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L97 ANSWER 48 OF 150 MEDLINE on STN DUPLICATE 34  
 TI Absence of inducible nitric oxide synthase modulates early  
 reperfusion-induced NF-kappaB and AP-1 activation and enhances myocardial

damage.

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L97 ANSWER 49 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

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SO FASEB JOURNAL, (MAR 2002) Vol. 16, No. 3, pp. 327-342.  
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ISSN: 0892-6638.

AU Zingarelli B (Reprint); Hake P W; Yang Z Q; O'Connor M; Denenberg A; Wong H R

AN 2002:315512 SCISEARCH

L97 ANSWER 50 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Regulation of macrophage cytokine and chemokine production by adipocyte fatty acid binding protein (aP2).

SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A319. print.  
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CODEN: FAJOEC. ISSN: 0892-6638.

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AN 2002:353805 BIOSIS

L97 ANSWER 51 OF 150 MEDLINE on STN DUPLICATE 35

TI Characterization of the bovine IkappaB kinases (IKK)alpha and IKKbeta, the regulatory subunit NEMO and their substrate IkappaBalpha.

SO GENE, (2002 Oct 16) 299 (1-2) 293-300.  
Journal code: 7706761. ISSN: 0378-1119.

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L97 ANSWER 52 OF 150 MEDLINE on STN DUPLICATE 36

TI Role of glycogen synthase kinase-3 in TNF-alpha-induced NF-kappaB activation and apoptosis in hepatocytes.

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CS D.A. Brenner, Univ. of North Carolina, Dept. of Medicine, CB #7038, Chapel Hill, NC 27599, United States.  
E-mail: dab@med.unc.edu

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DT Journal; Article

CY United States

LA English

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L97 ANSWER 54 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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 factor in prostate carcinoma cells  
 SO Journal of Cell Science (2002), 115(1), 141-151  
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 AN 2002:88316 HCAPLUS  
 DN 136:260512

L97 ANSWER 55 OF 150 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V. on STN  
 TI Development of a sensitive immunoradiometric assay for detection of  
 platelet surface-associated immunoglobulins in thrombocytopenic dogs  
 SO American Journal of Veterinary Research, (01 JAN 2002), 63/1 (124-129),  
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 CODEN: AJVRAH ISSN: 0002-9645  
 AU Scott M.A.; Kaiser L.; Davis J.M.; Schwartz K.A.  
 AN 2002:35100466 BIOTECHNO

L97 ANSWER 56 OF 150 MEDLINE on STN DUPLICATE 37  
 TI A novel affinity gene fusion system allowing protein A-based recovery of  
 non-immunoglobulin gene products.  
 SO JOURNAL OF BIOTECHNOLOGY, (2002 Oct 9) 99 (1) 41-50.  
 Journal code: 8411927. ISSN: 0168-1656.  
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 Stahl Stefan  
 AN 2002448151 MEDLINE

L97 ANSWER 57 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
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 Vol. 2002, pp. Abstract No. 388.2. <http://sfn.scholarone.com>. cd-rom.  
 Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.  
 Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.  
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 [Reprint Author]  
 AN 2003:294867 BIOSIS

L97 ANSWER 58 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
 TI Novel antiinflammatory compound comprising membrane translocation domain  
 fused to NEMO binding sequence, useful for blocking nuclear factor kappaB  
 activation, and for treating asthma, lung inflammation, psoriasis;  
 involving vector plasmid pBIIX-mediated gene transfer for expression  
 in HeLa cell culture, for use in drug screening and therapy  
 AU MAY M J; GHOSH S; FINDEIS M A; PHILLIPS K  
 AN 2002-05632 BIOTECHDS  
 PI WO 2001083554 8 Nov 2001

L97 ANSWER 59 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
 TI Modulating NF-kappaB induction in a cell, useful for treating e.g.  
 inflammatory disorders, osteoporosis and cancer, comprises contacting a  
 cell with an anti-inflammatory compound comprising at least one NEMO  
 binding domain;  
 transcription factor induction, membrane translocation domain and NEMO  
 binding peptide domain useful for disease therapy, diagnosis and drug  
 screening  
 AU MAY M J; GHOSH S  
 AN 2002-09696 BIOTECHDS  
 PI WO 2001083547 8 Nov 2001

L97 ANSWER 60 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
 TI Novel isolated nucleic acid molecule encoding isolated I $\kappa$ B-kinase binding  
 protein designated Y2H35, useful as probes and primers in molecular

biology and biotechnology;  
recombinant protein production via plasmid expression in host cell  
useful in gene therapy

AU Marcu K B  
AN 2001-10472 BIOTECHDS  
PI US 6214582 10 Apr 2001

L97 ANSWER 61 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 41  
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treatment of insulin resistance  
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CODEN: PIXXD2

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WO 2001010384	A3	20010607		
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AU 2000068987	A5	20010305	AU 2000-68987	20000810

L97 ANSWER 62 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI Inhibitor of the inflammatory response induced by the TNFA and IL-1.  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
(July 24, 2001) Vol. 1248, No. 4. e-file.  
CODEN: OGUPE7. ISSN: 0098-1133.

AU Greene, Warner C. [Inventor]; Lin, Xin [Inventor, Reprint author];  
Gelezuinas, Romas [Inventor]  
AN 2001:447244 BIOSIS

L97 ANSWER 63 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI I $\kappa$ B kinase, subunits thereof, and methods of using same.  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
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CODEN: OGUPE7. ISSN: 0098-1133.

AU Karin, Michael [Inventor]; DiDonato, Joseph A. [Inventor, Reprint author];  
Rothwarf, David M. [Inventor]; Hayakawa, Makio [Inventor]; Zandi, Ebrahim  
[Inventor]  
AN 2001:524963 BIOSIS

L97 ANSWER 64 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI IKK- $\alpha$  proteins, nucleic acids and methods.  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
(May 22, 2001) Vol. 1246, No. 4. e-file.  
CODEN: OGUPE7. ISSN: 0098-1133.

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[Inventor]  
AN 2001:514405 BIOSIS

L97 ANSWER 65 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI IKK- $\alpha$  proteins, nucleic acids and methods.  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
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CODEN: OGUPE7. ISSN: 0098-1133.

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L97 ANSWER 66 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
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 CODEN: OGUPE7. ISSN: 0098-1133.  
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 Catherine [Inventor]  
 AN 2001:514732 BIOSIS

L97 ANSWER 67 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI IKK- $\beta$ -based method for identifying compounds for treatment of insulin  
 resistance  
 SO U.S. Pat. Appl. Publ., 11 pp., Cont.-in-part of U.S. Ser. No. 636,150.  
 CODEN: USXXCO  
 IN Shoelson, Steven  
 AN 2001:798710 HCAPLUS  
 DN 135:327359

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	US 6630312	B2	20031007		
	US 6468755	B1	20021022	US 2000-636150	20000810
	US 2003044852	A1	20030306	US 2002-269553	20021011

L97 ANSWER 68 OF 150 MEDLINE on STN DUPLICATE 42  
 TI IKKgamma /NEMO facilitates the recruitment of the IkappaB proteins into  
 the IkappaB kinase complex.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Sep 28) 276 (39) 36327-36.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 AU Yamamoto Y; Kim D W; Kwak Y T; Prajapati S; Verma U; Gaynor R B  
 AN 2001522210 MEDLINE

L97 ANSWER 69 OF 150 MEDLINE on STN DUPLICATE 43  
 TI Complete reconstitution of human IkappaB kinase (IKK) complex in yeast.  
 Assessment of its stoichiometry and the role of IKKgamma on the complex  
 activity in the absence of stimulation.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Sep 28) 276 (39) 36320-6.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 AU Miller B S; Zandi E  
 AN 2001522209 MEDLINE

L97 ANSWER 70 OF 150 MEDLINE on STN DUPLICATE 44  
 TI Effects of the NIK aly mutation on NF-kappaB activation by the  
 Epstein-Barr virus latent infection membrane protein, lymphotoxin beta  
 receptor, and CD40.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 May 4) 276 (18) 14602-6.  
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L97 ANSWER 84 OF 150 MEDLINE on STN DUPLICATE 55  
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L97 ANSWER 87 OF 150 MEDLINE on STN DUPLICATE 58  
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CODEN: IMFREG; ISSN: 0917-0774  
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L97 ANSWER 91 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 60  
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ISSN: 0270-9139.  
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L97 ANSWER 94 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
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AN 2002:201052 BIOSIS

L97 ANSWER 95 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
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recombinant protein production in host cell for antiinflammatory and immunosuppressive activity  
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AN 2000-11099 BIOTECHDS  
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L97 ANSWER 101 OF 150 MEDLINE on STN DUPLICATE 67  
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L97 ANSWER 102 OF 150 MEDLINE on STN DUPLICATE 68  
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L97 ANSWER 103 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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L97 ANSWER 104 OF 150 MEDLINE on STN DUPLICATE 69  
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L97 ANSWER 105 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN  
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CODEN: GEDEEP; ISSN: 0890-9369  
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L97 ANSWER 107 OF 150 MEDLINE on STN DUPLICATE 70  
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L97 ANSWER 108 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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SO Molecular Medicine (Tokyo) (2000), 37(2), 144-150  
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AN 2000:94334 HCAPLUS  
DN 133:55735

L97 ANSWER 109 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
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expression in host cell, DNA probe, DNA primer and antibody, used for  
diagnosis and therapy  
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AN 1999-04021 BIOTECHDS  
PI WO 9901541 14 Jan 1999

L97 ANSWER 110 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
DUPLICATE 72  
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L97 ANSWER 111 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 73  
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recombinant expression, and use in treating inflammation and in  
identifying anti-inflammatory drugs  
SO PCT Int. Appl., 46 pp.  
CODEN: PIXXD2  
IN Chu, Keting; Pot, David  
AN 1999:464103 HCAPLUS  
DN 131:84843

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 9934000	A1	19990708	WO 1998-US27917	19981230
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,			

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,  
 CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 US 6030834 A 20000229 US 1998-215131 19981218  
 AU 9920242 A1 19990719 AU 1999-20242 19981230

L97 ANSWER 112 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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 IL-1

SO PCT Int. Appl., 48 pp.

CODEN: PIXXD2

IN Greene, Warner C.; Lin, Xin; Gelezuinas, Romas

AN 1999:566073 HCAPLUS

DN 131:198629

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943704	A1	19990902	WO 1999-US4110	19990225
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9928778	A1	19990915	AU 1999-28778	19990225
US 6265538	B1	20010724	US 1999-257703	19990225
US 2002042499	A1	20020411	US 2001-871889	20010601

L97 ANSWER 113 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI Cloning and expression of cDNA for human low-molecular-weight G  
 protein-activating **Spa-1** protein

SO PCT Int. Appl., 80 pp.

CODEN: PIXXD2

IN Minato, Nagahiro

AN 1999:166645 HCAPLUS

DN 130:192794

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910380	A1	19990304	WO 1998-JP3715	19980821
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887488	A1	19990316	AU 1998-87488	19980821
JP 11137283	A2	19990525	JP 1998-250344	19980821

L97 ANSWER 114 OF 150 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
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 polypeptides and their **binding** targets.

PI US 5916760 A 19990629 (199932)\* 14p C12P001-48

IN GOEDEL, D V; WORONICZ, J

L97 ANSWER 115 OF 150 MEDLINE on STN DUPLICATE 74

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 inhibition of I-kappaB kinase.

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Journal code: 2985121R. ISSN: 0021-9258.

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L97 ANSWER 116 OF 150 MEDLINE on STN DUPLICATE 75

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 mediates interaction of IKK with the human T-cell leukemia virus Tax  
 protein.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Aug 13) 274 (33) 22911-4.

Journal code: 2985121R. ISSN: 0021-9258.  
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AN 1999367408 MEDLINE

L97 ANSWER 117 OF 150 MEDLINE on STN DUPLICATE 76  
TI Rap1 GTPase-activating protein **SPA-1** negatively  
regulates cell adhesion.  
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L97 ANSWER 118 OF 150 MEDLINE on STN DUPLICATE 77  
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Human T-cell leukemia virus type I Tax interacts directly with IkappaB  
kinase gamma.  
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Journal code: 2985121R. ISSN: 0021-9258.  
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AN 1999292691 MEDLINE

L97 ANSWER 119 OF 150 MEDLINE on STN DUPLICATE 78  
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TBK1, a novel IKK-related kinase.  
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L97 ANSWER 120 OF 150 MEDLINE on STN DUPLICATE 79  
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L97 ANSWER 121 OF 150 MEDLINE on STN DUPLICATE 80  
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L97 ANSWER 124 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

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 ISSN: 0006-4971.  
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L97 ANSWER 125 OF 150 MEDLINE on STN DUPLICATE 83  
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L97 ANSWER 127 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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L97 ANSWER 128 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE  
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L97 ANSWER 130 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN  
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L97 ANSWER 131 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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L97 ANSWER 133 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 86  
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DN 129:213855

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PI	WO 9837228	A1	19980827	WO 1998-US3511	19980223
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6268194	B1	20010731	US 1997-810131	19970225
	AU 9866646	A1	19980909	AU 1998-66646	19980223
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	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001524813	T2	20011204	JP 1998-536953	19980223
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L97 ANSWER 134 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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PI	US 5831024	A	19981103	US 1995-380403	19950130
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L97 ANSWER 135 OF 150 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
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L97 ANSWER 138 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
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L97 ANSWER 140 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
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L97 ANSWER 146 OF 150 MEDLINE on STN DUPLICATE 94  
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L97 ANSWER 147 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
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CODEN: JKXXAF  
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AN 1989:232268 HCAPLUS  
DN 110:232268

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PI	JP 63315148	A2	19881222	JP 1987-150111	19870618
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L97 ANSWER 148 OF 150 MEDLINE on STN DUPLICATE 95

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L97 ANSWER 149 OF 150 MEDLINE on STN DUPLICATE 96  
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L97 ANSWER 150 OF 150 MEDLINE on STN  
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COST IN U.S. DOLLARS                SINCE FILE      TOTAL
                                     ENTRY      SESSION
FULL ESTIMATED COST                166.04      166.52
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=> save temp l97 ikk/a
ANSWER SET NOT SAVED.
THE ANSWER SET WAS CREATED IN FILES 'MEDLINE, SCISEARCH, LIFESCI,
BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, ESBIODBASE, BIOTECHNO, WPIDS'.
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To use the SAVE command, you must be in the same file environment in
which the answer set was created.
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=> fil .bec
COST IN U.S. DOLLARS                SINCE FILE      TOTAL
                                     ENTRY      SESSION
FULL ESTIMATED COST                1.50      168.02
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 ESBIODBASE, BIOTECHNO, WPIDS' ENTERED AT 16:06:06 ON 04 NOV 2003  
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11 FILES IN THE FILE LIST

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ANSWER SET L97 HAS BEEN SAVED AS 'IKK/A'
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,101-104,107,114,117,119,120,122,123,125,134,139,143,145,146
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L73 ANSWER 6 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB We report that the product of the inducible gene encoding the kinase known as IKKi/IKK $\epsilon$  (IKKi) is required for expression of a group of genes up-regulated by pro-inflammatory stimuli such as bacterial endotoxin (lipopolysaccharide (LPS)). Here, using murine embryonic fibroblasts obtained from mice bearing deletions in IKK2, p65, and IKKi genes, we provide evidence to support a link between signaling through the NF- $\kappa$ B and C/EBP $\beta$ /enhancer-binding protein (C/EBP) pathways. This link includes an NF- $\kappa$ B-dependent regulation of C/EBP $\beta$  and C/EBP $\delta$  gene transcription and IKKi-mediated activation of C/EBP. Disruption of the NF- $\kappa$ B pathway results in the blockade of the inducible up-regulation of C/EBP $\beta$ , C/EBP $\delta$ , and IKKi genes. Cells lacking IKKi are normal in activation of the canonical NF- $\kappa$ B pathway but fail to induce C/EBP $\delta$  activity and transcription of C/EBP and C/EBP-NF- $\kappa$ B target genes in response to LPS. In addition we show that, in response to LPS or tumor necrosis factor  $\alpha$ , both  $\beta$  and  $\delta$  subunits of C/EBP interact with IKKi promoter, suggesting a feedback mechanism in the regulation of IKKi-dependent cellular processes. These data are among the first to provide insights into the biol. function of IKKi.

L73 ANSWER 7 OF 150 MEDLINE on STN

DUPLICATE 3

AB In the present study, we showed that **SPA-1**, a Rap1 GTPase-activating protein (GAP), was bound to a cytoskeleton-anchoring protein AF-6. **SPA-1** and AF-6 were co-immunoprecipitated in the 293T cells transfected with both cDNAs as well as in normal thymocytes. In vitro **binding** studies using truncated fragments and their mutants suggested that **SPA-1** was bound to the PDZ domain of AF-6 via probable internal PDZ ligand motif within the GAP-related domain. The motif was conserved among Rap1 GAPs, and it was shown that rapGAP 1 was bound to AF-6 comparably with **SPA-1**. RapV12 was also bound to AF-6 via the N-terminal domain, and **SPA-1** and RapV12 were co-immunoprecipitated only in the presence of AF-6, indicating that they could be brought into close proximity via AF-6 in cells. Immunostaining analysis revealed that **SPA-1** and RapV12 were co-localized with AF-6 at the cell attachment sites. In HeLa cells expressing **SPA-1** in a tetracycline-regulatory manner, expression of AF-6 inhibited endogenous Rap1GTP and beta(1) integrin-mediated cell adhesion to fibronectin in **SPA-1**-induced conditions, whereas it affected neither of them in **SPA-1**-repressed conditions. These results suggested that AF-6 could control integrin-mediated cell adhesion by regulating Rap1 activation through the recruitment of both **SPA-1** and Rap1GTP via distinct domains.

L73 ANSWER 10 OF 150 MEDLINE on STN

DUPLICATE 6

AB When expressed in heterologous cells, the viral FLIP protein (vFLIP) of Kaposi's-sarcoma-associated herpesvirus (KSHV) has been reported both to block Fas-mediated apoptosis and to activate the NF-kappaB activation pathway by interaction with IkappaB kinase (IKK). In a yeast-two-hybrid screen, we identified IKKgamma as an interacting partner of vFLIP. We expressed fragments of IKKgamma in mammalian cells and bacteria, and identified the central CCR3/4 (amino acids 150-272) as the vFLIP binding region. To investigate the proteins interacting with vFLIP in a KSHV-infected primary effusion lymphoma (PEL) cell line, we immunoprecipitated vFLIP and identified four associated proteins by mass spectrometry: IKK components IKKalpha, beta and gamma, and the chaperone, Hsp90. Using gel filtration chromatography, we demonstrated that a single population of vFLIP in the cytoplasm of PEL cells co-eluted and co-precipitated with an activated IKK complex. An inhibitor of Hsp90, geldanamycin, inhibited IKK's kinase activity induced by vFLIP and killed PEL cells, suggesting that vFLIP activation of IKK contributes to PEL cell survival.

- L73 ANSWER 21 OF 150 MEDLINE on STN DUPLICATE 15  
 AB The transcription factors interferon regulatory factor 3 (IRF3) and NF-kappaB are required for the expression of many genes involved in the innate immune response. Viral infection, or the binding of double-stranded RNA to Toll-like receptor 3, results in the coordinate activation of IRF3 and NF-kappaB. Activation of IRF3 requires signal-dependent phosphorylation, but little is known about the signaling pathway or kinases involved. Here we report that the noncanonical IkappaB kinase homologs, IkappaB kinase-epsilon (**IKKepsilon**) and TANK-binding kinase-1 (TBK1), which were previously implicated in NF-kappaB activation, are also essential components of the IRF3 signaling pathway. Thus, IKKepsilon and TBK1 have a pivotal role in coordinating the activation of IRF3 and NF-kappaB in the innate immune response.
- L73 ANSWER 24 OF 150 MEDLINE on STN DUPLICATE 17  
 AB Nuclear factor kappaB (NF-kappaB) plays a pivotal role in numerous cellular processes, including stress response, inflammation, and protection from apoptosis. Therefore, the activity of NF-kappaB needs to be tightly regulated. We have previously identified a novel gene, named CIKS (connection to IkappaB-kinase and SAPK), able to **bind** the regulatory sub-unit NEMO/**IKKgamma** and to activate NF-kappaB. Here, we demonstrate that CIKS forms homo-oligomers, interacts with NEMO/IKKgamma, and is recruited to the IKK-complex upon cell stimulation. In addition, we identified the regions of CIKS responsible for these functions. We found that the ability of CIKS to oligomerize, and to be recruited to the IKK-complex is not sufficient to activate the NF-kappaB. In fact, a deletion mutant of CIKS able to oligomerize, to interact with NEMO/IKKgamma, and to be recruited to the IKK-complex does not activate NF-kappaB, suggesting that CIKS needs a second level of regulation to efficiently activate NF-kappaB.
- L73 ANSWER 25 OF 150 MEDLINE on STN DUPLICATE 18  
 AB Leucine zipper-bearing kinase (LZK) is a novel member of the mixed lineage kinase (MLK) family [Sakuma, H., Ikeda, A., Oka, S., Kozutsumi, Y., Zanetta, J. P., and Kawasaki, T. (1997) J. Biol. Chem. 272, 28622-28629]. We have previously shown that LZK activates the c-Jun-NH2 terminal kinase (JNK) pathway, but not the extracellular signal-related kinase (ERK) pathway, by acting as a mitogen-activated protein kinase kinase kinase (MAPKKK) [Ikeda, A., Hasegawa, K., Masaki, M., Moriguchi, T., Nishida, E., Kozutsumi, Y., Oka, S., and Kawasaki, T. (2001) J. Biochem. 130, 773-781]. However, the mode of activation of LZK remains largely unknown. By means of a yeast two-hybrid screening system, we have identified a molecule localized to mitochondria, antioxidant protein-1 (AOP-1), that binds to LZK and which acts as a modulator of LZK activity. Recently, several MAPKKKs involved in the JNK pathway, such as MEKK1, TAK1 and MLK3, were shown, using over-expression assay systems, to activate a transcription factor, NF-kappaB, through activation of the IKK complex. Using similar assay systems, we demonstrated that LZK activated NF-kappaB-dependent transcription through IKK activation only weakly, but this was reproducible, and that AOP-1 enhanced the LZK-induced NF-kappaB activation. We also provided evidence that LZK was associated directly with the IKK complex through the kinase domain, and that AOP-1 was recruited to the **IKK** complex through the **binding** to LZK.
- L73 ANSWER 26 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 19
- L73 ANSWER 28 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
 AB DERWENT ABSTRACT:  
 NOVELTY - A new isolated protein complex (I) comprises two proteins, and selected from a complex of a first protein and a second protein; a complex of a fragment of the first protein and second protein; a complex

of the first protein and a fragment of the second protein; or a complex of a fragment of the first protein and a fragment of the second protein.

DETAILED DESCRIPTION - The first and second proteins of (I) are selected from: (a) the first protein is **IKKb** and the second protein is selected from LDHM, EIF3S10, SLAP2, KIAA0614, SART-1 and GBDR1; (b) the first protein is **IKKa** and the second protein is GBDR1; (c) the first protein is **IKKg** and the second protein is TRAF; or (d) the first protein is **IKK-i** and the second protein is selected from NUMA1, **SPA-1** and PN13730.

INDEPENDENT CLAIMS are also included for the following: (1) an isolated antibody selectively immunoreactive with (I); (2) a method for diagnosing a physiological disorder in an animal; (3) a method for determining whether a mutation in a gene encoding one of the proteins of (I) is useful for diagnosing a physiological disorder; (4) a non-human animal model for a physiological disorder where the genome of the animal or its ancestor has been modified such that the formation of (I) has been altered; (5) a cell line obtained from the animal model of (4); (6) a non-human animal model for a physiological disorder, wherein the biological activity of (I) has been altered; (7) a cell in which the genome of cells of the cell line has been modified to produce or eliminate at least one (I); (8) a composition comprising a first and second expression vector; (9) a host cell comprising a first and second expression vector; (10) a method for screening for drug candidates capable of modulating the interaction of the proteins of (I); (11) a drug useful for treating a physiological disorder identified by the method of (10); (12) a method of screening for drug candidates useful in treating a physiological disorder; (13) a drug useful for treating a physiological disorder identified by the method of (12); (14) a method for selecting modulators of a protein complex formed between a first protein or its homologue, derivative or fragment, and a second protein or its homologue, derivative or fragment, where the first and second proteins are from (I); (15) a modulator useful for treating a physiological disorder identified by the method of (14); (16) a method for selecting modulators of an interaction between a first protein and a second protein, the first protein or its homologue, derivative or fragment and the second protein or its homologue, derivative or fragment, where the first and second proteins are from (I); (17) a modulator useful for treating a physiological disorder identified by the method of (16); (18) a method for identifying a compound that **binds** to a protein in vitro, where the protein is from (I); (19) a compound useful for treating a physiological disorder identified by the method of (19); (20) a method for selecting modulators of a protein, where the protein is from (I), the method comprising contacting the protein with a test compound, and determining **binding** of the test compound to the protein; (21) an inhibitor useful for treating a physiological disorder identified by the method of (16); (22) a method for modulating in a cell, a protein complex having a first protein interacting with a second protein, where the first and second proteins are from (I); (23) a method for modulating, in a cell, the interaction of a protein with a ligand, where the protein is from the first or second proteins of (I); (24) a method for modulating neuronal death in a patient having a physiological disorder; (25) a method for treating a physiological disorder; (26) a method of modulating activity in a cell of a protein, the protein being first protein or a second protein from (I); (27) an isolated nucleic acid selected from: (a) a sequence encoding a protein comprising a fully defined sequence of 494 amino acids (P1), given in the specification, or its complement; (b) a sequence encoding a protein comprising at least 70% identical to P1, and which is capable of interacting with **IKK-i**; (c) a sequence comprising a sequence at least 60% identical to nucleotides 152-1633 of a sequence of 1633 bp (N1), fully defined in the specification, or its complement; (d) a sequence comprising N1, or its complement; (e) a sequence comprising a contiguous span of at least 17 nucleotides of N1, or its complement; (f) a sequence comprising at least 21 nucleotides that encodes a contiguous span of at least 7 amino acids of P1; (28) nucleic

acid vectors comprising the isolated nucleic acid of (27); (29) host cells comprising the isolated nucleic acid of (27); (30) an isolated polypeptide selected from: (a) a polypeptide comprising P1; (b) a sequence at least 70% identical to P1, and which is capable of interacting with **IKK-i**; (c) a polypeptide comprising a contiguous span of at least 8 amino acids of P1; (d) a polypeptide comprising a sequence of 4-30 amino acids that is at least 75% identical to a contiguous span of P1, where the isolated polypeptide is capable of interacting with **IKK-i**; (31) an antibody which is specifically immunoreactive with the isolated polypeptide of (30); (32) a microarray comprising the isolated nucleic acid of (27); (33) a protein microarray comprising the isolated polypeptide of (30); and (34) a method for making the polypeptide of (30).

**BIOTECHNOLOGY - Preferred Protein complex:** (I) comprises the first and second protein. The protein complex further comprises a fragment of the first protein and the second protein or the first protein and a fragment of the second protein. The protein complex alternatively comprises fragments of the first protein and the second protein.

**Preferred Antibody:** The antibody is preferably a monoclonal antibody.

**Preferred Method:** The method of (2) comprises assaying for whether (I) is present in a tissue extract, the ability of proteins to form (I), and a mutation in a gene encoding a protein of (I). The method of (3) comprises assaying for the ability of the protein with the mutation to form a complex with the other protein of the protein complex, wherein an inability to form the complex is indicative of the mutation being useful for diagnosing a physiological disorder. The animal in the methods of (2) and (3) is a human. The physiological disorder is selected from inflammatory disease, rheumatoid arthritis, osteoarthritis, asthma, arteriosclerosis, inflammatory bowel disease or cancer. The diagnosis is for a predisposition to or for the existence of the physiological disorder. The assay comprises a yeast two-hybrid assay. The assay comprises measuring in vitro a complex formed by combining the proteins of the protein complex, the proteins isolated from the animal, where the complex is measured by **binding** with an antibody specific for the complex. The assay further comprises mixing an antibody specific for the protein complex with a tissue extract from the animal and measuring the **binding** of the antibody. The method of (10) comprises: (a) combining the proteins of the protein complex in the presence of a drug to form a first complex; (b) combining the proteins in the absence of the drug to form a second complex; (c) measuring the amount of the first complex and the second complex; and (d) comparing the amount of the first complex with the amount of the second complex, where if the amount of the first complex is greater than, or less than the amount of the second complex, then the drug is a drug candidate for modulating the interaction of the proteins of the protein complex. The screening is an in vitro screening. The complex is measured by **binding** with an antibody specific for the protein complexes. The amount of the first complex is greater than the amount of the second complex, then the drug is a drug candidate for promoting the interaction of the proteins. The amount of the first complex is less than the amount of the second complex, then the drug is a drug candidate for inhibiting the interaction of the proteins. The method of (12) comprises: (a) measuring the activity of a protein selected from the group consisting of a first protein and a second protein in the presence of a drug, where the first and second proteins are from (I); (b) measuring the activity of the protein in the absence of the drug; and (c) comparing the activity measured in (a) and (b), where if there is a difference in activity, then the drug is a drug candidate for treating the physiological disorder. The method of (14) comprises providing the protein complex; contacting the protein complex with a test compound, and determining the presence or absence of **binding** of the test compound to the protein complex. Alternatively, the method of (14) comprises contacting the protein complex with a test compound, and determining the interaction between the first and second protein. At least one of the first and second proteins

is a fusion protein having a detectable tag. The step of determining the interaction between the first protein and the second protein is conducted in a substantially cell free environment. The interaction between the first protein and the second protein is determined in a host cell, where the host cell is a yeast cell. The test compound is provided in a phage display library or a combinatorial library. The method of (16) comprises contacting the first protein with the second protein in the presence of a test compound, and determining the interaction between the first protein and the second protein. Alternatively, the method of (16) comprises: (a) providing in a host cell a first fusion protein having the first polypeptide, and a second fusion protein having the second polypeptide, where a DNA **binding** domain is fused to one of the first and second polypeptides while a transcription-activating domain is fused to the other of the first and second polypeptides; (b) providing in the host cell a reporter gene, where the transcription of the reporter gene is determined by the interaction between the first polypeptide and the second polypeptide; (c) allowing the first and second fusion proteins to interact with each other within the host cell in the presence of a test compound; and (d) determining the presence or absence of expression of the reporter gene. Alternatively, the method of (16) comprises providing atomic coordinates defining a three-dimensional structure of a protein complex formed by the first polypeptide and the second polypeptide, and designing or selecting compounds capable of modulating or interfering with the interaction between a first polypeptide and a second polypeptide based on the atomic coordinates. The method of (18) comprises contacting a test compound with the protein for a time sufficient to form a complex, and detecting for the formation of a complex by detecting the protein or the compound in the complex, so that if a complex is detected, a compound that **binds** to protein is identified. The test compound in the method of (20) is provided in a phage display library or a combinatorial library. The method of (22) comprises administering to the cell a compound capable of modulating the protein complex or a peptide capable of interfering with interaction between the first and second protein, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. The method of (23) comprises administering to the cell a compound capable of modulating the interaction. The method of (24) comprises modulating a protein complex having a first protein interacting with a second protein, where the first and second proteins are from (I), or administering to the patient a compound capable of modulating a protein complex having a first protein interacting with a second protein, where the first and second proteins are from (I), or a peptide capable of interfering with interaction between the first and second protein, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. The method of (25) comprises administering to the cell a compound capable of modulating a protein complex having a first protein interacting with a second protein, wherein the first and second proteins are from (I), or a peptide capable of interfering with the interaction between a first protein and a second protein, wherein the first and second proteins are from (I), where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. The method of (26) comprises administering to the cell a compound capable of modulating the protein, or administering to the cell a peptide having a contiguous span of at least 4 amino acids of one of the first or second proteins and capable of **binding** the other of the first or second proteins, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. The compound in the methods of (22)-(26) is selected from: (a) a compound which interferes with the interaction between the first and second protein; (b) a compound which **binds** to the protein or ligand; (c) a compound which comprises a peptide having a contiguous span of amino acids of at least 4 amino acids of the protein and capable of **binding** the ligand; (d) a compound which comprises a peptide capable of **binding** the ligand and having an amino acid sequence of 4-30 amino acids that is at least 75% identical to

a contiguous span of amino acids of the protein of the same length; (e) a compound which is an antibody immunoreactive with the protein or ligand; (f) a compound which modulates the expression of the protein or ligand; (g) a compound which is an antisense compound or a ribozyme specifically hybridizing to a nucleic acid encoding the ligand or protein or their complement; (h) a compound which is capable of **binding** at least one of the first protein and the second protein; (i) a compound which comprises a peptide having a contiguous span of amino acids of at least 4 amino acids of a second protein and capable of **binding** a first or second protein; and (j) a compound which is an antisense compound or a ribozyme specifically hybridizing to a nucleic acid encoding a first protein or second protein or their complement. The peptide in the methods of (22), (24), (25) and (26) is covalently linked to the transporter which is selected from penetratins, l-Tat49-57, d-Tat49-57, retro-inverso isomers of l- or d-Tat49-57, L-arginine oligomers, D-arginine oligomers, L-lysine oligomers, D-lysine oligomers, L-histidine oligomers, D-histidine oligomers, L-ornithine oligomers, D-ornithine oligomers, short peptide sequences derived from fibroblast growth factor, Galparan and HSV-1 structural protein VP22 and peptide analogs. The physiological disorder in the methods of (23) and (25) is selected from inflammatory disease, rheumatoid arthritis, osteoarthritis, asthma, arteriosclerosis, inflammatory bowel disease or cancer. The method of (34) comprises providing an expression vector with a nucleic acid encoding the amino acid sequence, and introducing the expression vector into a host cell such that the host cell is producing the isolated polypeptide. Preferred Animal Model: The physiological disorder in the non-human animal model of (4) is selected from inflammatory disease, rheumatoid arthritis, osteoarthritis, asthma, arteriosclerosis, inflammatory bowel disease or cancer. The formation of the protein complex has been altered as a result of: (a) over-expression of at least one of the proteins of the protein complex; (b) replacement of a gene for at least one of the proteins of the protein complex with a gene from a second animal and expression of the protein; (c) expression of a mutant form of at least one of the proteins of the protein complex; (d) a lack of expression of at least one of the proteins of the protein complex; or (e) reduced expression of at least one of the proteins of the protein complex. The biological activity of the non-human animal model of (6) has been altered as a result of disrupting the formation of the complex or disrupting the action of the complex. The formation of the complex is disrupted by **binding** an antibody to at least one of the proteins which form the protein complex. The action of the complex is disrupted by **binding** an antibody to the complex. The formation of the complex is alternatively disrupted by **binding** a small molecule to at least one of the proteins which form the protein complex. The action of the complex is disrupted by **binding** a small molecule to the complex. Preferred Composition: The first expression vector in the composition of (8) has a nucleic acid encoding a first protein or its homologue, derivative or fragment, and the second expression vector having a nucleic acid encoding a second protein or its homologue, derivative or fragment, where the first and the second proteins are the proteins of (I). Preferred Host Cell: The first expression vector in the host cell of (9) has a nucleic acid encoding a first protein or its homologue, derivative or fragment, and the second expression vector having a nucleic acid encoding a second protein or its homologue, derivative or fragment, where the first and the second proteins are the proteins of (I). The host cell is preferably a yeast cell. The first and second proteins are expressed in fusion proteins. One of the first and second nucleic acids is preferably linked to a nucleic acid encoding a DNA **binding** domain, and the other of the first and second nucleic acids is linked to a nucleic acid encoding a transcription-activation domain, whereby two fusion proteins can be produced in the host cell. The host cell further comprising a reporter gene, where the expression of the reporter gene is determined by the interaction between the first protein and the second protein. Preferred Nucleic Acid: The nucleic acid of (27) further comprises at

least 21, 25, 30 or 50 nucleotides. The nucleic acid of (27) further comprises encoding at least 8, 9, 10, 15, 20 or 25 contiguous amino acids. Preferred Polypeptide: The polypeptide of (30) further comprises a contiguous span of at least 10, 12, 15, 17 or 20 amino acids, capable of interacting with **IKK-i**. The amino acid sequence in the polypeptide further comprises 8-20 amino acids.

ACTIVITY - Antiinflammatory; Antirheumatic; Antiarthritic; Antidiabetic; Nootropic; Neuroprotective; Osteopathic; Antiasthmatic; Antiarteriosclerotic; Cytostatic. Test protocols are described but no results are given.

MECHANISM OF ACTION - Gene therapy; TNF-Agonist; Interleukin-Agonist-1.

USE - The methods and compositions of the present invention are useful for the diagnosis and/or treatment of physiological disorders involved in the protein-protein interaction, such as inflammatory disease, rheumatoid arthritis, diabetes, neurodegenerative disorders, osteoarthritis, asthma, arteriosclerosis, inflammatory bowel disease or cancer. The drugs, modulators, inhibitor or compounds are useful for treating the diseases described above (claimed).

EXAMPLE - The cDNA encoding the bait protein was generated by polymerase chain reaction (PCR) from brain cDNA. Gene-specific primers were synthesized with appropriate tails added at their 5' ends to allow recombination into the vector pGBTQ. In the yeast J693 cells, each cDNA was expressed as a fusion protein with the transcription activation domain of the transcription factor Gal4 and a 9 amino acid hemagglutinin epitope tag. J693 cells expressing the bait were then mated with J692 cells expressing proteins from the brain library. The resulting diploid yeast cells expressing proteins interacting with the bait protein were selected for the ability to synthesize tryptophan, leucine, histidine and beta-galactosidase. (61 pages)

L73 ANSWER 30 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
AB DERWENT ABSTRACT:

NOVELTY - An isolated polypeptide (I) comprises at least 10 consecutive residues of a 745 amino acid sequence, given in the specification, where the residues comprise at least one amino acid residue of 679, 680, 684, 686 and 687, or residue 543, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) screening for an agent which modulates the interaction of an **IKK** polypeptide to a **binding** target, comprising:  
(a) incubating a mixture with a (I), a binding target of the polypeptide and a candidate agent, under conditions where, but for the presence of the agent, the polypeptide specifically binds the binding target at a reference affinity; and (b) detecting the binding affinity of the polypeptide to the binding target to determine an agent-biased affinity, where a difference between the agent-biased affinity and the reference affinity indicates that the agent modulates the binding of the polypeptide to the binding agent; and (2) screening for an agent which modulates the ability of an **IKK** polypeptide to specifically phosphorylate an **IkB** polypeptide, comprising: (a) incubating a mixture with a (I) retaining kinase activity, an **IkB** polypeptide having at least a six residue domain of a natural **IkB** with at least one of Ser32 and Ser36, and a candidate agent, under conditions where but for the presence of the agent, the polypeptide specifically phosphorylates the **IkB** polypeptide at at least one of the Ser32 and Ser36 at a reference activity; and (b) detecting the polypeptide-induced phosphorylation of the **IkB** polypeptide at at least one of the Ser32 and Ser36 to determine an agent-biased activity, where a difference between the agent-biased activity and the reference activity indicates that the agent modulates the ability of the polypeptide to specifically phosphorylate an **IkB** polypeptide.

WIDER DISCLOSURE - Nucleic acids, expression vectors, probes, primers and host cells used in the methods of the invention.

BIOTECHNOLOGY - Preferred Polypeptide: (I) has a kinase or kinase inhibitory activity, a **NIK**-binding or binding inhibitory activity, an

IkB-binding or binding inhibitory activity and an NFkB activating or inhibitory activity. The consecutive amino acid residues comprise the amino acid residue 679, 680, 684, 686, 687, 540-548, 543-550, 536-543, 534-554, 533-543, 543-563, 542-549, 538-545, 541-547, 403-543 or 543-604 of a 745 amino acid sequence, given in the specification. Preferred Method: The binding target in the method of (1) is a natural intracellular substrate and the reference and agent-biased binding affinity is detected as phosphorylation of the substrate.

ACTIVITY - Neuroprotective; Immunostimulant. No biological data is given.

MECHANISM OF ACTION - Kinase-Inhibitor; Kinase-Stimulator.

USE - The methods and compositions of the present invention are useful for the diagnosis and treatment of disorders associated with the aberrant activity of the IKK polypeptide, such as signal transduction disorders, genetic defects and autoimmune diseases.

EXAMPLE - An expression vector was generated that encodes NIK fused to the DNA-binding domain of the yeast transcription factor GAL4, and was used as a bait in a two-hybrid screen of a human B cell cDNA library. Eight positive clones were obtained, and one encoded a novel protein, IKK-alpha that comprise an N-terminal serine-threonine kinase catalytic domain, a C-terminal helix-loop-helix domain and a leucine zipper-like amphipathic a-helix juxtaposed in between the helix-loop-helix and kinase domain. (15 pages)

L73 ANSWER 32 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
AB DERWENT ABSTRACT:

NOVELTY - An isolated nucleic acid molecule that encodes an I kappa B protein kinase having a kinase domain, no leucine zipper like alpha-helix domain, and no helix-loop-helix domain, where the I kappa B protein kinase has kinase activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated nucleic acid molecule that hybridizes under high stringent conditions to the nucleic acid cited above; and (2) making an I kappa B protein kinase having a kinase domain, no leucine zipper like alpha-helix domain, and no helix-loop-helix domain by expressing in a host cell the nucleic acid molecule.

WIDER DISCLOSURE - Also disclosed as new are: (1) screening for an agent that modulates I kappa B phosphorylation by the I kappa B kinase that has kinase domain and has neither a leucine zipper like alpha-helix domain nor a helix-loop helix domain; (2) isolated nucleic acid molecules that encode IKKalpha-deltaLH or IKKalpha-deltaCm; (3) antisense nucleic acids sequences and degenerate sequences for the above nucleic acid molecules; (4) isolated I kappa B protein; and (5) antibodies that **bind** to the epitopes found on **IKKalpha-deltaLH**.

BIOTECHNOLOGY - Isolation: The nucleic acid was isolated from a murine cDNA library using IKKalpha/CHUK specific probes. The I kappa B protein is prepared by standard recombinant techniques. Preferred Molecule: The nucleic acid molecule comprises a kinase domain that is a serine/threonine kinase domain. The kinase domain of the protein is at least 65% identical to the kinase domain of a fully defined sequence of 451 amino acids, given in the specification. The kinase domain is encoded by a DNA that hybridizes under highly stringent conditions to a nucleic acid molecule that is complementary to a fully defined sequence of 1406 bp, given in the specification. The nucleic acid molecule further encodes the sequence of: Ile-Phe-Arg-Lys-Asn-Val-Lys-Ser-Met-Glu-Arg-Asn-Gly-Arg-Lys-Gly-His-Ser-Leu-Phe. The nucleic acid molecule comprises a fully defined sequence of 1406, 3314 or 1874 bp, given in the specification, or comprises a sequence that is at least 30% identical to these sequences.

ACTIVITY - Antiinflammatory; Immunomodulator; Anti-HIV. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The nucleic acid molecule is useful for treating inflammation or immune diseases and for regulating the progression of AIDS or allograft rejection.

EXAMPLE - Screening for several murine cDNA libraries with IKK $\alpha$ /CHUK specific probes produced multiple isolates of three IKK $\alpha$ /CHUK cDNAs with overlapping and different structural features. (32 pages)

L73 ANSWER 36 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB The IKK $\beta$  and NEMO/IKK $\gamma$  subunits of the NF- $\kappa$ B-activating signalsome complex are known to be essential for activating NF- $\kappa$ B by inflammatory and other stress-like stimuli. However, the IKK $\alpha$  subunit is believed to be dispensable for the latter responses and instead functions as an in vivo mediator of other novel NF- $\kappa$ B-dependent and -independent functions. In contrast to this generally accepted view of IKK $\alpha$ 's physiologic functions, we demonstrate in mouse embryonic fibroblasts (MEFs) that, akin to IKK $\beta$  and NEMO/IKK $\gamma$ , IKK $\alpha$  is also a global regulator of tumor necrosis factor  $\alpha$ - and IL-1-responsive IKK signalsome-dependent target genes including many known NF- $\kappa$ B targets such as serum amyloid A3, C3, interleukin (IL)-6, IL-11, IL-1 receptor antagonist, vascular endothelial growth factor, Ptx3,  $\beta$ 2-microglobulin, IL-1 $\alpha$ , MCP-1 and -3, RANTES (regulated on activation normal T cell expressed and secreted), Fas antigen, Jun-B, c-Fos, macrophage colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor. Only a small number of NF- $\kappa$ B-dependent target genes were preferentially dependent on IKK $\alpha$  or IKK $\beta$ . Constitutive expression of a trans-dominant I $\kappa$ B $\alpha$  superrepressor (I $\kappa$ B $\alpha$ SR) in wild type MEFs confirmed that these signalsome-dependent target genes were also dependent on NF- $\kappa$ B. A subset of NF- $\kappa$ B target genes were IKK-dependent in the absence of exogenous stimuli, suggesting that the signalsome was also required to regulate basal levels of activated NF- $\kappa$ B in established MEFs. Overall, a sizable number of novel NF- $\kappa$ B/IKK-dependent genes were identified including Secreted Frizzled, cadherin 13, protocadherin 7, CCAAT/enhancer-binding protein- $\beta$  and - $\delta$ , osteoprotegerin, FOXO2 and FOXO3, BMP-2, p75 neurotrophin receptor, caspase-11, guanylate-binding proteins 1 and 2, ApoJ/clusterin, interferon ( $\alpha$  and  $\beta$ ) receptor 2, decorin, osteoglycin, epiregulin, proliferins 2 and 3, stromal cell-derived factor, and cathepsins B, F, and Z. SOCS-3, a neg. effector of STAT3 signaling, was found to be an NF- $\kappa$ B/IKK-induced gene, suggesting that IKK-mediated NF- $\kappa$ B activation can coordinately illicit neg. effects on STAT signaling.

L73 ANSWER 38 OF 150 MEDLINE on STN DUPLICATE 26

AB Canonical activation of NF-kappa B is mediated via phosphorylation of the inhibitory I kappa B proteins by the I kappa B kinase complex (IKK). IKK is composed of a heterodimer of the catalytic IKK alpha and IKK beta subunits and a presumed regulatory protein termed NEMO (NF-kappa B essential modulator) or IKK gamma. NEMO/IKK gamma is indispensable for activation of the IKKs in response to many signals, but its mechanism of action remains unclear. Here we identify TANK (TRAF family member-associated NF-kappa B activator) as a NEMO/IKK gamma-interacting protein via yeast two-hybrid analyses. This interaction is confirmed in mammalian cells, and the domains required are mapped. TANK was previously shown to assist NF-kappa B activation in a complex with TANK-binding kinase 1 (TBK1) or IKK epsilon, two kinases distantly related to IKK alpha/beta, but the underlying mechanisms remained unknown. Here we show that TBK1 and IKK epsilon synergize with TANK to promote interaction with the IKKs. The TANK binding domain within NEMO/IKK gamma is required for proper functioning of this IKK subunit. These results indicate that TANK can synergize with IKK epsilon or TBK1 to link them to IKK complexes, where the two kinases may modulate aspects of NF-kappa B activation.

L73 ANSWER 41 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB Nuclear factor- $\kappa$ B activation depends on phosphorylation and degradation of its inhibitor protein, I $\kappa$ B. The phosphorylation of

I $\kappa$ B $\alpha$  on Ser32 and Ser36 is initiated by an I $\kappa$ B kinase (IKK) complex that includes a catalytic heterodimer composed of I $\kappa$ B kinase 1 (IKK-1) and I $\kappa$ B kinase 2 (IKK-2) as well as a regulatory adaptor subunit, NF- $\kappa$ B essential modulator. Recently, two related I $\kappa$ B kinases, TBK-1 and IKK-i, have been described. TBK-1 and IKK-i show sequence and structural homol. to IKK-1 and IKK-2. TBK-1 and IKK-i phosphorylate Ser36 of I $\kappa$ B $\alpha$ . We describe the kinetic mechanisms in terms of substrate and product inhibition of the recombinant human (rh) proteins, rhTBK-1, rhIKK-1, and rhIKK-1/rhIKK-2 heterodimers. The results indicate that although each of these enzymes exhibits a random sequential kinetic mechanism, the effect of the binding of one substrate on the affinity of the other substrate is significantly different. ATP has no effect on the binding of an I $\kappa$ B $\alpha$  peptide for the rhIKK-1/rhIKK-2 heterodimer ( $\alpha$  = 0.99), whereas the binding of ATP decreased the affinity of the I $\kappa$ B $\alpha$  peptide for both rhTBK-1 ( $\alpha$  = 10.16) and rhIKK-i ( $\alpha$  = 62.28). Furthermore, the dissociation consts. of ATP for rhTBK-1 and rhIKK-i are between the expected values for kinases, whereas the dissociation consts. of the I $\kappa$ B $\alpha$  peptide for each IKK isoforms is unique with rhTBK-1 being the highest (KI $\kappa$ B $\alpha$  = 69.87  $\mu$ M), followed by rhIKK-i (KI $\kappa$ B $\alpha$  = 5.47  $\mu$ M) and rhIKK-1/rhIKK-2 heterodimers (KI $\kappa$ B $\alpha$  = 0.12  $\mu$ M). Thus this family of I $\kappa$ B kinases has very unique kinetic properties.

L73 ANSWER 43 OF 150 MEDLINE on STN DUPLICATE 30  
 AB Activation of T cells by antigen requires adhesive interactions with antigen-presenting cells (APC) in which leukocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecules (ICAMs) are important. However, it is not well understood what signaling molecules regulate this process and how the modulation of adhesive events influences T-cell activation. Here we show that Rap1 is activated in T cells in an antigen-dependent manner and accumulated at the contact site of T-cell and antigen-loaded APC. Inhibition of Rap1 activation by a dominant-negative Rap1 or **SPA-1**, a Rap1 GTPase-activating protein, abrogates LFA-1-ICAM-1-mediated adhesive interactions with antigen-pulsed APC and the subsequent T-cell-receptor triggering and interleukin-2 production. Conversely, augmented antigen-dependent Rap1 activation by the expression of wild-type Rap1 enhances these responses but culminates in apoptosis by Fas and FasL. Thus, Rap1 functions as a key regulator of T-cell and APC interactions and modulates T-cell responses from productive activation to activation-induced cell death by regulating the strength of adhesive interactions. Moreover, constitutive Rap1 activation rendered T cells unresponsive with accumulation of p27(Kip1). Our study indicates that the activation state of Rap1 has a decisive effect on the T-cell response to antigen.

L73 ANSWER 44 OF 150 MEDLINE on STN DUPLICATE 31  
 AB BACKGROUND: The PSD-95 family of proteins possesses multiple protein **binding** domains, including three PDZ domains, an SH3 domain, a HOOK domain and a guanylate kinase-like (GK) domain. The PSD-95 proteins function as scaffolding proteins that link ion channels such as the N-methyl-d-aspartate-receptors (NMDA-Rs) with cytoskeletal networks and signalling molecules, thereby controlling synaptic plasticity and learning. RESULTS: We found that the PSD-95 family proteins interact via their GK domains with **SPA-1**-like protein (SPAL), a GTPase-activating protein (GAP) that is specific for Rap1. SPAL was contained within the NMDA-R-PSD-95 complex, and co-localized with PSD-95 and NMDA-R at the synapses in cultured hippocampal neurones. Furthermore, NMDA stimulation induced the dephosphorylation of SPAL in cultured hippocampal neurones. CONCLUSION: Our findings suggest that SPAL may be involved in the NMDA-mediated organization of cytoskeletal networks and signal transduction.

L73 ANSWER 51 OF 150 MEDLINE on STN DUPLICATE 35

AB The Nuclear factor (NF)-kappaB signalling pathway plays a critical role in the regulation and coordination of a wide range of cellular events such as cell growth, apoptosis and cell differentiation. Activation of the IKK (inhibitor of NF-kappaB kinase) complex is a crucial step and a point of convergence of all known NF-kappaB signalling pathways. To analyse bovine IKKalpha (IKK1), IKKbeta (IKK2) and IKKgamma (or NF-kappaB Essential MOdulator, NEMO) and their substrate IkappaBalpha (Inhibitor of NF-kappaB), the corresponding cDNAs of these molecules were isolated, sequenced and characterized. A comparison of the amino acid sequences with those of their orthologues in other species showed a very high degree of identity, suggesting that the IKK complex and its substrate IkappaBalpha are evolutionarily highly conserved components of the NF-kappaB pathway. Bovine IKKalpha and IKKbeta are related protein kinases showing 50% identity which is especially prominent in the kinase and leucine zipper domains. Co-immunoprecipitation assays and GST-pull-down experiments were carried out to determine the composition of bovine IKK complexes compared to that in human Jurkat T cells. Using these approaches, the presence of bovine IKK complexes harbouring IKKalpha, IKKbeta, NEMO and the interaction of IKK with its substrate IkappaBalpha could be demonstrated. Parallel experiments using human Jurkat T cells confirmed the high degree of conservation also at the level of protein-protein interactions. Finally, a yeast two-hybrid analysis showed that bovine NEMO molecules, in addition to the **binding** to **IKKalpha** and **IKKbeta**, also strongly interact with each other.

L73 ANSWER 54 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB Rel/NF- $\kappa$ B transcription factors are implicated in the control of cell proliferation, apoptosis and transformation. The key to NF- $\kappa$ B regulation is the inhibitory I $\kappa$ B proteins. During response to diverse stimuli, I $\kappa$ Bs are rapidly phosphorylated by I $\kappa$ B kinases (IKKs), ubiquitinated and undergo degradation. The authors have investigated the expression and function of NF- $\kappa$ B, I $\kappa$ B inhibitors and IKKs in normal prostate epithelial cells and prostate carcinoma (PC) cell lines LNCaP, MDA PCa 2b, DU145, PC3, and JCA1. The authors found that NF- $\kappa$ B was constitutively activated in human androgen-independent PC cell lines DU145, PC3, JCA1 as well as androgen-independent CL2 cells derived from LNCaP. In spite of a strong difference in constitutive  $\kappa$ B binding, Western blot anal. did not reveal any significant variance in the expression of p50, p65, I $\kappa$ Bs, IKK $\beta$ , and IKK $\alpha$  between primary prostate cells, androgen-dependent and androgen-independent PC cells. However, the authors found that in androgen-independent PC cells I $\kappa$ B $\alpha$  was heavily phosphorylated and displayed a faster turnover. Using an in vitro kinase assay the authors demonstrated constitutive activation of IKK in androgen-independent PC cell lines. Blockage of NF- $\kappa$ B activity in PC cells by dominant-neg. I $\kappa$ B $\alpha$  resulted in increased constitutive and TNF $\alpha$ -induced apoptosis. These data suggest that increased IKK activation leads to the constitutive activation of NF- $\kappa$ B "survival signaling" pathway in androgen-independent PC cells. This may be important for the support of their androgen-independent status and growth advantage.

L73 ANSWER 57 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AB Transcriptional dysregulation and enhanced susceptibility to excitotoxicity of medium spiny neurons (MSNs) have been implicated in the pathogenesis of Huntingtons disease (HD). It is not known if these two mechanisms are related, however. We find that the NF- $\kappa$ B transcriptional pathway is activated by mutant huntingtin protein (Htt) in PC12 cells. Activation is mediated by physical interaction between mutant Htt exon-1 and IKKg, a regulatory component of the I $\kappa$ B kinase complex (IKK). This interaction results in activation of the IKK complex, involving phosphorylation and degradation of the inhibitory protein I $\kappa$ B. A recombinant antibody specific for the polyproline domain of Htt interferes



H-RRMKWKKKTALDWSWLQTE-NH<sub>2</sub>; H-YGRRKKRRQRRRTALDWSWLQTE-NH<sub>2</sub>;  
H-rrrrrrrrTALDWSWLQTE-NH<sub>2</sub>; H-YARKARRQARRTALDWSWLQTE-NH<sub>2</sub>;  
H-YARAARRAARRTALDWSWLQTE-NH<sub>2</sub>; H-RRMKWKKLDWSWL-NH<sub>2</sub>; H-rrmkwkkLDWSWL-NH<sub>2</sub>;  
H-rrrrrrrrLDWSWL-NH<sub>2</sub>; H-YARAARRAARRLDWSWL-NH<sub>2</sub>; H-yaraarraarrLDWSWL-NH<sub>2</sub>;  
H-YGRKKRRQRRRLDWSWL-NH<sub>2</sub>.

**ACTIVITY** - Antiinflammatory; antiasthmatic; cytostatic; antipsoriatic; antirheumatic; antiarthritic; osteopathic; antibacterial; immunosuppressive; dermatological; neuroprotective; nootropic; antiatherosclerotic; virucide; antiallergic. The NBD peptide was tested for its ability to inhibit inflammatory responses in animals using two distinct models of acute inflammation. In the first model, ear edema was induced in mice using phorbol-12-myristate-13-acetate (PMA) and the effects of topical administration of the NBD peptides were measured. Twenty  $\mu$ l of either NBD peptides (200  $\mu$ g/ear), dexamethasone (40  $\mu$ g/ear) or vehicle (DMSO:Ethanol; 25:75 v/v) was applied topically to the right ear of mice thirty minutes before and thirty minutes after the application of 20  $\mu$ l of PMA (5  $\mu$ g/ear) dissolved in ethanol. Ear swelling was measured six hours after PMA application a microgauge and expressed as the mean difference in thickness between the treated (right) and untreated (left) ears. Statistical analysis of the data was performed using the students t-test. The results showed that the wild-type peptide significantly reduced (77+/-3% inhibition) PMA-induced ear thickening to the level observed with dexamethasone (82+/-9% inhibition). In contrast, the effect observed with an equivalent dose of mutant was insignificant. In a second model, peritonitis was induced in mice by intraperitoneal (i.p.) injection of zymosan either alone or in combination with dexamethasone or the NBD peptides. Groups of animals were injected concomitantly with one ml zymosan (1 mg/ml) and either dexamethasone (100 mg/ml) or the NBD peptides (200 mg/ml). The concentration of NOX (nitrate plus nitrite) present in the inflammatory exudates was measured using a colorimetric assay kit according to the manufacturers protocol. Results showed that zymosan injection caused an accumulation of inflammatory exudate fluids and migration of polymorphonuclear cells (PMN) into the peritoneum of these animals. Treatment of mice with wild-type NBD peptide or dexamethasone significantly reduced exudate formation and PMN accumulation whereas the mutant had no effect.

**MECHANISM OF ACTION** - Selective inhibitor of cytokine-mediated NF $\kappa$ B activation by blocking interaction of IkappaB kinase beta ( **IKKbeta**) at the NEMO **binding** domain that results in inhibition of IKKbeta kinase activation and subsequent decreased phosphorylation of IkappaB; blocker of the recruitment of leukocytes into sites of acute and chronic inflammation, by downregulating expression of E-selection on leukocytes, or by blocking osteoclast differentiation; inflammation modulator.

**USE** - (I) is useful for treating an inflammatory disorder e.g., asthma, lung inflammation or cancer in a subject. (I) is also useful for treating inflammatory disorders such as psoriasis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, sepsis, vasculitis, bursitis; autoimmune diseases such as lupus, polymyalgia, scleroderma, granulomatosis, multiple sclerosis; transplant rejection; osteoporosis; Alzheimer's disease; atherosclerosis; viral infections; and ataxia telangiectasia. (I) is also useful for treating pro-inflammatory responses such as allergies e.g., allergic rhinitis, urticaria, anaphylaxis, drug or food sensitivity; eczema, dermatitis, sunburn, aging, etc; arthritis such as spondylarthritis, psoriatic arthritis, etc. (I) is also used for inhibiting NF $\kappa$ B-dependent target gene expression in a cell, and for inhibiting NF $\kappa$ B induction.

**ADMINISTRATION** - (I) is administered by oral, intramuscular, subcutaneous, intravenous, buccal, transdermal, rectal, colonic, vaginal, intranasal or respiratory tract route. Dosages range from 0.001-30 (more preferably, 5-6) mg/kg body weight.

**EXAMPLE** - To identify the NEMO-interacting domain of IkappaB kinase beta (IKKbeta), an in vitro pull down assay was performed using a bacterially expressed version of full length NEMO fused at its

NH2-terminus to glutathione S-transferase (GST-NEMO). Various truncation mutants lacking different functional domains of IKKbeta (catalytic domain, leucine zipper and helix-loop-helix (HLH)) were constructed. All sub-cloning and mutagenesis of full length cDNA clones of IKKalpha and IKKbeta was performed by PCR using cloned Pfu DNA-polymerase. The wild-type and mutated IKKbeta cDNA were inserted into the KpnI and NotI restriction sites of pcDNA-3 or pcDNA-3.1-xpress and all IKKalpha cDNAs were inserted into the EcoRI and XhoI sites of the same vectors. FLAG-tagged versions of both kinases were constructed by subcloning into pFLAG-CMV-2. For GST-IKKbeta-(644-756), the PCR fragment was inserted into the EcoRI and XhoI sites of pGEX-4T1. Full length cDNA encoding human NEMO was obtained by reverse transcriptase (RT)-PCR from HeLa cell mRNA. These mutants were labeled by in vitro translation with (35S)-methionine mixed with either GST alone or GST-NEMO, and precipitated using glutathione-agarose. None of the mutants interacted with GST alone, whereas wild-type and all three NH2-terminal truncations of IKKbeta (307-756, 458-756 and 486-756) interacted with GST-NEMO. In contrast, none of the COOH-terminal truncation mutants (1-456, 1-605 or 1-644) precipitated with GST-NEMO. These results demonstrated that NEMO interacted with a region in the COOH-terminus of IKKbeta distal to the HLH domain. A mutant consisting of only the region from amino acid 644 (immediately after the HLH) to the COOH-terminus (residue 756) of IKKbeta was constructed next and this mutant did not precipitate with GST but did interact with GST-NEMO confirming that this region mediated the interaction between these two molecules. The effects of IKKbeta-(644-756) on interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha-induced NF-kappaB activation by transiently transfecting HeLa cells with the mutant together with an NF-kappaB-dependent reporter plasmid (pBIIIX-luciferase) was tested next. For transfection studies, HeLa and COS cells were grown for twenty-four hours before transfection of DNA. Cells received a total of 1 mug or 2 mug of DNA, respectively. After forty-eight hours cells were lysed with TNT (200 mM NaCl, 20 mM Tris-pH 8.0, 1% Triton-100) and the lysate were used for either immunoprecipitation or luciferase assay. IKKbeta-(644-756) inhibited NF-kappaB activation induced by these cytokines in a dose-dependent manner. These results indicated that IKKbeta-(644-756) acts as a dominant-negative by titrating endogenous NEMO out of the core IkappaB-kinase complex. Without the recruitment of regulatory proteins by NEMO, IKKbeta became refractory to IL-1beta- and TNFalpha-induced signals that should otherwise cause its activation. Also it was demonstrated that IKKbeta-(644-756) interacted with NEMO-(1-196), -(1-302) and -(44-419) but not NEMO-(197-419) but not NEMO-(197-419) or -(86-419). Identical results were obtained from immuno-precipitation studies using lysate of COS or HEK293 cells transiently transfected with FLAG-tagged IKKbeta and the NEMO mutants. These results established that the interaction domain lies between residues 44 and 86, a region including the first alpha-helix of NEMO. A mutant was therefore made in which alpha-helix up to the first coiled-coil domain was deleted (residues T50-L93; del.alphaH). This mutant did not interact with IKKbeta-(644-756). Furthermore transfection studies using pBIIIX-luciferase demonstrated that del.alphaH inhibited TNF-alpha-induced NF-kappaB activity confirming that the COOH-terminus of NEMO which can not interact with IKKbeta, was a dominant-negative inhibitor of NF-kappaB. To fully characterize the NEMO-interaction domain of IKKbeta further truncation mutants between residues V644 and S756 were constructed. Immediately after the HLH, the amino acid sequence to the cysteine at position 662 exhibited 72% identity with IKKalpha. Following this, the region up to E707 was a serine-rich domain previously reported to be a target for auto-phosphorylation and to function in down-regulating IKKbeta activity after stimulation by pro-inflammatory cytokines. The sequence succeeding this contained no serine residues until position 733. Mutants sequentially omitting each of these regions were (35S)-methionine-labeled and used in GST-pull-down assays. None of the IKKbeta mutants precipitated with GST-NEMO and indicating that the interaction domain resides in the extreme COOH-terminus between residues

F734 and S756. Further experiments carried out showed that basal auto-phosphorylation and kinase activity of IKKbeta was dependent on the ability of NEMO to associate with the kinase and that in the absence of NEMO, IKKbeta became auto-phosphorylated, basally active and refractory to TNFalpha-induced signals indicating that NEMO played a fundamental role in the down-regulation as well as activation of IKKbeta activity. (88 pages)

L73 ANSWER 59 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN  
AB DERWENT ABSTRACT:

NOVELTY - (1) Modulating NF-kappaB (NF-kB) induction in a cell comprises contacting a cell with an anti-inflammatory compound (I) comprising at least one NEMO binding domain.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (2) treating a subject suffering from an inflammatory disorder comprising administering (I) to the subject; (3) modulating NF-kB-dependent target gene expression in a cell comprising contacting a cell with an (I) comprising at least one NEMO binding domain; (4) identifying a compound capable of interacting with NEMO, comprising exposing cells which express NEMO and NF-kB to a test compound and determining whether the test compound modulates activation of NF-kB by the cell, where an alteration in activation of NF-kB is indicative of a compound which is capable of interacting with NEMO; (5) identifying a compound which modulates an activity of NEMO, comprising exposing cells which express NEMO to a test compound and determining whether the test compound modulates an activity of NEMO, thereby identifying a compound which modulates an activity of NEMO; (6) (I) comprising a NEMO binding domain fused with at least one membrane translocation domain; (7) a composition comprising (I) as in (6); (8) an isolated peptide selected from: (a) an isolated peptide comprising the amino acid sequence of SEQ ID NO:2 to 19 given in the specification; (b) an isolated peptide comprising a fragment of at least three amino acids of the amino acid sequence of SEQ ID NO:2 to 19 given in the specification; (c) an isolated peptide comprising a conservative amino acid substitution in the amino acid sequence of SEQ ID NO:2 to 19 given in the specification; and (d) a naturally occurring amino acid sequence variant of the amino acid sequence of SEQ ID NO:2 to 19 given in the specification. (9) an isolated peptide consisting of the amino acid sequence of SEQ ID NO:2 to 19 given in the specification; (10) a composition comprising the peptide in (8) or (9); (11) an isolated nucleic acid molecule selected from: (a) an isolated nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO: 2 to 19 given in the specification; and (b) an isolated nucleic acid molecule that encodes a fragment of at least three amino acids of SEQ ID NO: 2 to 19 given in the specification; (12) treating an NF-kB-mediated condition in a subject comprising administering an (I) which inhibits **binding** of NEMO to an **IKK** (IkappaB kinase); (13) an (I) comprising the amino acid sequence DRQIKIWFQNRRMKWKKTALDWSWLQTE.

ACTIVITY - Antiinflammatory; immunosuppressive; osteopathic; cytostatic; nootropic; neuroprotective; antiarteriosclerotic; virucide; antiasthmatic; antiallergic; dermatological; antibacterial; antipsoriatic; antirheumatic; antiarthritic; osteopathic; antiulcer; anti-HIV.

MECHANISM OF ACTION - Selective inhibition of cytokine-mediated NF-kB activation by blocking the interaction of NEMO with **IKKbeta** at the NEMO **binding** domain. Blockage of **IKKbeta**-NEMO interaction results in inhibition of IKKbeta kinase activation and subsequent decreased phosphorylation of IkappaB. (I) may also act (directly or indirectly) by blocking the recruitment of leukocytes into sites of acute and chronic inflammation, by down-regulating the expression of E-selectin on leukocytes, or by blocking osteoclast differentiation.

USE - In (12), the NF-kB-mediated condition is an inflammatory disorder, an autoimmune disease, transplant rejection, osteoporosis,

cancer, Alzheimer's disease, atherosclerosis, a viral infection, or ataxia telangiectasia. The inflammatory disorder is asthma, allergies, urticaria, anaphylaxis, cutaneous inflammation, sepsis, psoriasis, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, vasculitis and bursitis. The inflammatory disorder may also be dermatitis, eczema, psoriasis, osteoarthritis, psoriatic arthritis, lupus and spondylarthritis (all claimed). Also for Crohn's disease, ulcerative colitis, polymyalgia, scleroderma, Wegner's granulomatosis, temporal arteritis, cryoglobulinemia or multiple sclerosis. For chronic viral infections such as caused by Epstein-barr, cytomegalovirus or herpes simplex. Other viral diseases include HIV and influenza. (I) may also be useful for treating anaphylaxis, drug and food sensitivity; contact dermatitis, sunburn or aging. (I) may be used to replace corticosteroids in any application in which corticosteroids are used, including immunosuppression in transplants and cancer therapy. Also for identifying antiinflammatory compounds and for diagnosis of an inflammatory disorder. (I) may be administered alone or in combination with other known anti-inflammatory agents.

**ADMINISTRATION** - Administration is parenteral or oral, by intramuscular injection, subcutaneous/intradermal injection, intravenous injection, buccal, transdermal, rectal, colonic, vaginal, intranasal or by respiratory tract route (e.g. by inhalation). Dosage is 0.001-30 (preferably 0.01-25, especially 0.1-20, particularly 5-6) mg/kg. Dosage for systemic administration is 0.01-100 (preferably 0.1-10) mg/kg/day.

**ADVANTAGE** - While blocking NF-kB induction via IKK, (I) do not inhibit the basal activity of NF-kB.

**EXAMPLE** - The NEMO binding domain (NBD) peptide was tested for its ability to inhibit inflammatory responses in animals using two distinct models of acute inflammation. In the first model, ear edema was induced in mice using phorbol-12-myristate-13-acetate (PMA) and the effects of topical administration of the NBD peptides measured. Ear edema using PMA was induced in replicate groups of age and sex matched mice as previously described (Chang et al., (1 987) Eur. J. Pharmacol. 142, 197-205). 20 microl of either NBD peptides (200 microg/ear), dexamethasone (40 microg/ear) or vehicle (DMSO:Ethanol; 25:75 v/v) was applied topically to the right ear of mice thirty minutes before and thirty minutes after the application of 20 microl of PMA (5 microg/ear) dissolved in ethanol. Ear swelling was measured six hours after PMA application using a microgauge and expressed as the mean difference in thickness between the treated (right) and untreated (left) ears. Statistical analysis of the data was performed using the students t-test. A value of p less than 0.05 was considered statistically significant. Figure 6A shows that the wild type peptide significantly reduced (77 +/- 3% inhibition; p less than 0.05) PMA-induced ear thickening to the level observed with dexamethasone (82 +/- 9% inhibition; p less than 0.05). In contrast, the effect observed with an equivalent dose of mutant was insignificant (p = 0.09). Neither peptide had an effect when administered in the absence of PMA (not shown). (57 pages)

L73 ANSWER 61 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 41

AB A method is provided for identifying, evaluating, or making a compound or agent, e.g., a candidate compound or agent, for treatment of a disorder characterized by insulin resistance. The method includes evaluating the ability of a compound or agent to interact with, e.g. **bind**, **IKK- $\beta$** , to thereby identify a compound or agent for the treatment of a disorder characterized by insulin resistance. The invention also features compds. for treating insulin resistance identified by such methods, and methods of treating a subject having a disorder characterized by insulin resistance by administering such agents.

L73 ANSWER 67 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB A method is disclosed for identifying, evaluating, or making a compound or agent, e.g., a candidate compound or agent, for treatment of a disorder

characterized by insulin resistance. The method includes evaluating the ability of a compound or agent to **bind IKK- $\beta$**  or modulate **IKK- $\beta$**  activity, to thereby identify a compound or agent for the treatment of a disorder characterized by insulin resistance. The invention also discloses compds. for treating insulin resistance identified by such methods, and methods of treating a subject having a disorder characterized by insulin resistance by administering such agents.

- L73 ANSWER 68 OF 150 MEDLINE on STN DUPLICATE 42  
AB IKKgamma/NEMO is an essential regulatory component of the IkappaB kinase complex that is required for NF-kappaB activation in response to various stimuli including tumor necrosis factor-alpha and interleukin-1beta. To investigate the mechanism by which IKKgamma/NEMO regulates the IKK complex, we examined the ability of IKKgamma/NEMO to recruit the IkappaB proteins into this complex. **IKKgamma/NEMO binding** to wild-type, but not to a kinase-deficient IKKbeta protein, facilitated the association of IkappaBalpha and IkappaBbeta with the high molecular weight IKK complex. Following tumor necrosis factor-alpha treatment of HeLa cells, the majority of the phosphorylated form of endogenous IkappaBalpha was associated with the high molecular weight IKK complex in HeLa cells and parental mouse embryo fibroblasts but not in IKKgamma/NEMO-deficient cells. Finally, we demonstrate that IKKgamma/NEMO facilitates the association of the IkappaB proteins and IKKbeta and leads to increases in IKKbeta kinase activity. These results suggest that an important function of IKKgamma/NEMO is to facilitate the association of both IKKbeta and IkappaB in the high molecular weight IKK complex to increase IkappaB phosphorylation.
- L73 ANSWER 71 OF 150 MEDLINE on STN DUPLICATE 45  
AB The IL-1 receptor-associated kinase (IRAK/mPLK) is linked to the regulation of nuclear factor-kappaB (NF-kappaB)-dependent gene expression. Here we describe a novel binding partner of IRAK/mPLK that we term SIMPL (signaling molecule that associates with the mouse pelle-like kinase). Overexpression of SIMPL leads to the activation of NF-kappaB-dependent promoters, and inactivation of SIMPL inhibits IRAK/mPLK as well as tumor necrosis factor receptor type I-induced NF-kappaB activity. Dominant inhibitory alleles of IkappaB kinase (IKKalpha or IKKbeta) block the activation of NF-kappaB by IRAK/mPLK and SIMPL. Furthermore, SIMPL **binds** IRAK/mPLK and the **IKKs** in vitro and in vivo. In the presence of antisense mRNA to SIMPL, the physical association between IRAK/mPLK and IKKbeta but not IRAK/mPLK and IKKalpha is greatly diminished. Moreover, dominant-negative SIMPL blocks IKKalpha- or IKKbeta-induced NF-kappaB activity. These results lead us to propose a model in which SIMPL functions to regulate NF-kappaB activity by linking IRAK/mPLK to IKKbeta/alpha-containing complexes.
- L73 ANSWER 79 OF 150 MEDLINE on STN DUPLICATE 53  
AB Mechanical force or mechanical stress modulates intracellular signal pathways, including the mitogen-activated protein kinase (MAP kinase) cascades. In our system, cell stretching activated and cell contraction inactivated all three MAP kinase pathways (MKK1/2-extracellular signal-regulated kinase (ERK), MKK4 (SEK1)-cJun N-terminal kinase (JNK) and MKK3/6-p38 pathways). However, little is known about the molecular mechanisms that link the mechanical force to the MAP kinase cascades. To test whether Ras and Rap1 are possible components in the stretch-activated MAP kinase pathways, we examined if Ras and Rap1 were activated by cell stretching and if inhibition of their activity decreased the stretch-enhanced MAP kinase activity. Rap1 was activated by cell stretching and inactivated by cell contraction, whereas Ras was inactivated by cell stretching and activated by cell contraction. Rap1GapII and **SPA-1**, downregulators of Rap1 activity, decreased the stretch-enhanced p38 activity, whereas a dominant-negative mutant of Ras (RasN17) did not inhibit the stretch-initiated activation of MAP kinases. Furthermore, overexpression of Rap1 enhanced p38 activity

but not ERK or JNK activity. These results indicate that Rap1 is involved in transducing the stretch-initiated signal to the MKK3/6-p38 pathway, but not to the MEK1/2-ERK or the MKK4 (SEK1)/MKK7-JNK pathway. Thus, Rap1 plays a unique role in force-initiated signal transduction.

L73 ANSWER 83 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

L73 ANSWER 87 OF 150 MEDLINE on STN DUPLICATE 58

AB CD98 is a multifunctional heterodimeric membrane protein involved in the regulation of cell adhesion as well as amino acid transport. We show that CD98 cross-linking persistently activates Rap1 GTPase in a LFA-1-dependent manner and induces LFA-1/ICAM-1-mediated cell adhesion in lymphocytes. Specific phosphatidylinositol-3-kinase (PI3K) inhibitors suppressed both LFA-1 activation and Rap1GTP generation, and abrogation of Rap1GTP by retroviral over-expression of a specific Rap1 GTPase activating protein, **SPA-1**, totally inhibited the LFA-1/ICAM-1-mediated cell adhesion. These results suggest that CD98 cross-linking activates LFA-1 via the PI3K signaling pathway and induces accumulation of Rap1GTP in a LFA-1-dependent manner, which in turn mediates the cytoskeleton-dependent cell adhesion process.

L73 ANSWER 88 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB A review with 30 refs., on roles of Rap1 G protein in immune system and hematopoietic system, discussing functional regulation of integrins by Rap1, essential roles of Rap1 in T-cell activation via immunol. synapse formation, immunol. anergy and deficient T-cell memory generation in **SPA-1** (Rap1 GTPase-activating protein) gene-deficient mice, and chronic myelocytic leukemia-like diseases in **SPA-1** deficient mice.

L73 ANSWER 91 OF 150 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 60

AB Nuclear factor-kappaB (NF-kappaB) protects hepatocytes from undergoing apoptosis during embryonic development and during liver regeneration. Activation of NF-kappaB is mediated through phosphorylation of its inhibitor, I kappaB, by a kinase complex that contains 2 I kappaB kinases, We analyzed the differential role of I kappaB kinase 1 (IKK1) and I kappaB kinase 2 (IKK2) in tumor necrosis factor alpha (TNF-alpha)- and interleukin-1 beta (IL-1 beta)-mediated NF-kappaB activation in primary rat hepatocytes. Maximal induction of IKK activity was observed 5 minutes after TNF-alpha and 15 minutes after IL-1 beta treatment, and activated IKK was able to phosphorylate GST-I kappaB (1-54) and GST-p65 (354-551), but not a GST-p65 (354-551) substrate with a serine-to-alanine substitution at position 536. Infection with an adenovirus containing catalytically inactive IKK2K44M (Ad5IKK2dn) completely blocked both TNF-alpha and IL-1 beta -induced GST-I kappaB and GST-p65 phosphorylation, I kappaB degradation, and NF-kappaB DNA **binding**. Adenovirally transduced, catalytically inactive **IKK1K44M** (Ad5IKK1dn) reduced **IKK** activity and NF-kappaB DNA **binding** only slightly. Accordingly, Ad5IKK2dn induced apoptosis in 75% (+/-6%) of hepatocytes after 12 hours of TNF-alpha, which was accompanied by activation of caspases 3 and 8, nuclear fragmentation, and DNA laddering. In contrast, Ad5IKK1dn led to 21% (+/-2%) apoptosis in TNF-alpha -treated hepatocytes after 12 hours and comparatively low activity of caspases 3 and 8. Furthermore, Ad5IKK2dn completely blocked the induction of inducible nitric oxide synthase (iNOS), whereas Ad5IKK1dn had no influence on the expression of iNOS. Thus, IKK2 is the main mediator for cytokine-induced NF-kappaB activation in primary hepatocytes and protects against TNF-alpha -induced apoptosis, whereas IKK1 kinase activity is not required for NF-kappaB activation.

L73 ANSWER 94 OF 150 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

L73 ANSWER 95 OF 150 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN

AB A new isolated human DNA (I), with a fully defined 699 (NA2) or 678 (NA3) bp DNA sequence, encoding an isolated I kappa-B-kinase (**IKK**) **binding** protein (Y2H56) with a fully defined 226 (AA1) protein sequence, is claimed. Also claimed are: an isolated DNA molecule encoding an **IKK binding** protein that hybridizes under stringent conditions to (NA2) or (NA3); an isolated DNA molecule fully complementary to (NA2) or (NA3); methods of making an **IKK binding** protein or its allelic variants by incorporating (I) into a host cell ((I) is at least 85% identical to (NA2) or (NA3)), expressing (I), and isolating the **IKK binding** protein or its allelic variants. The protein is useful for detecting IKK complexes and modulating IKK activity in cells undergoing signaling by inflammatory mediators such as tumor necrosis factor and interleukin-1. IKK and its functional equivalents are also useful for identifying therapeutically active agents that modulate the binding or interaction of Y2H56 and either IKK-alpha or IKK-beta, useful for boosting the immune system, or as immunosuppressants, or as antiinflammatory agents. (9pp)

L73 ANSWER 101 OF 150 MEDLINE on STN DUPLICATE 67

AB Rap2 is a member of the Ras family of GTPases and exhibits 60% identity to Rap1, but the function and regulation of Rap2 remain obscure. We found that, unlike the other Ras family proteins, the GTP-bound active form exceeded 50% of total Rap2 protein in adherent cells. Guanine nucleotide exchange factors (GEFs) for Rap1, C3G, Epac (or cyclic AMP [cAMP]-GEF), CalDAG-GEF1, PDZ-GEF1, and GFR efficiently increased the level of GTP-Rap2 both in 293T cells and in vitro. GTPase-activating proteins (GAPs) for Rap1, rap1GAP1 and **SPA-1**, stimulated Rap2 GTPase, but with low efficiency. The half-life of GTP-Rap2 was significantly longer than that of GTP-Rap1 in 293T cells, indicating that low sensitivity to GAPs caused a high GTP/GDP ratio on Rap2. Rap2 bound to the Ras-**binding** domain of Raf and inhibited Ras-dependent activation of Elk1 transcription factor, as did Rap1. The level of GTP-Rap2 in rat 3Y1 fibroblasts was decreased by the expression of v-Src, and expression of a GTPase-deficient Rap2 mutant inhibited v-Src-dependent transformation of 3Y1 cells. Altogether, Rap2 is regulated by a similar set of GEFs and GAPs as Rap1 and functions as a slowly responding molecular switch in the Rap1 signaling cascade.

L73 ANSWER 102 OF 150 MEDLINE on STN DUPLICATE 68

AB Human T-cell leukemia virus type I (HTLV-I) Tax protein persistently stimulates the activity of I kappa B kinase (IKK), resulting in constitutive activation of the transcription factor NF-kappa B. Tax activation of IKK requires physical interaction of this viral protein with the IKK regulatory subunit, IKKgamma. The Tax/IKKgamma interaction allows Tax to engage the IKK catalytic subunits, IKKalpha and IKKbeta, although it remains unclear whether this linker function of IKKgamma is sufficient for supporting the Tax-specific IKK activation. To address this question, we have examined the sequences of IKKgamma required for modulating the Tax/IKK signaling. We demonstrate that when fused to Tax, a small N-terminal fragment of **IKKgamma**, containing its minimal **IKKalpha/beta-binding** domain, is sufficient for bringing Tax to and activating the IKK catalytic subunits. Disruption of the **IKKalpha/beta-binding** activity of this domain abolishes its function in modulating the Tax/IKK signaling. We further demonstrate that direct fusion of Tax to IKKalpha and IKKbeta leads to activation of these kinases. These findings suggest that the IKKgamma-directed Tax/IKK association serves as a molecular trigger for IKK activation.

L73 ANSWER 103 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN

AB The phosphorylation of I kappa B by the multiprotein I kappa B kinase complex (IKK) precedes the activation of transcription factor NF-kappa B, a key regulator of the inflammatory response. Here we identified the mixed-lineage group kinase 3 (MLK3) as an activator of NF-kappa B. Expression of the wild-type form of this mitogen-activated protein kinase

kinase kinase (MAPKKK) induced nuclear immigration, DNA binding, and transcriptional activity of NF- $\kappa$ B. MLK3 directly phosphorylated and thus activated I $\kappa$ B kinase alpha (IKK $\alpha$ ) and IKK $\beta$ , revealing its function as an I $\kappa$ B kinase kinase (IKKK). MLK3 cooperated with the other two IKKKs, MEKK1 and NF- $\kappa$ B-inducing kinase, in the induction of IKK activity. MLK3 bound to components of the IKC in vivo. This protein-protein interaction was dependent on the central leucine zipper region of MLK3. A kinase-deficient version of MLK3 strongly impaired NF- $\kappa$ B-dependent transcription induced by T-cell costimulation but not in response to tumor necrosis factor alpha or interleukin-1. Accordingly, endogenous MLK3 was phosphorylated and activated by T-cell costimulation but not by treatment of cells with tumor necrosis factor alpha or interleukin-1. A dominant neg. version of MLK3 inhibited NF- $\kappa$ B- and CD28RE/AP-dependent transcription elicited by the Rho family GTPases Rac and Cdc42, thereby providing a novel link between these GTPases and the IKC.

L73 ANSWER 104 OF 150 MEDLINE on STN DUPLICATE 69  
 AB Activation of the transcription factor nuclear factor (NF)-kappaB by proinflammatory stimuli leads to increased expression of genes involved in inflammation. Activation of NF-kappaB requires the activity of an inhibitor of kappaB (IkappaB)-kinase (IKK) complex containing two kinases (IKKalpha and IKKbeta) and the regulatory protein NEMO (NF-kappaB essential modifier). An amino-terminal alpha-helical region of NEMO associated with a carboxyl-terminal segment of IKKalpha and **IKKbeta** that we term the NEMO-**binding** domain (NBD). A cell-permeable NBD peptide blocked association of NEMO with the IKK complex and inhibited cytokine-induced NF-kappaB activation and NF-kappaB-dependent gene expression. The peptide also ameliorated inflammatory responses in two experimental mouse models of acute inflammation. The NBD provides a target for the development of drugs that would block proinflammatory activation of the IKK complex without inhibiting basal NF-kappaB activity.

L73 ANSWER 107 OF 150 MEDLINE on STN DUPLICATE 70  
 AB The adapter protein RIP plays a crucial role in NF-kappaB activation by TNF. Here we show that triggering of the p55 TNF receptor induces **binding** of RIP to NEMO (**IKKgamma**), a component of the I-kappa-B-kinase (IKK) "signalosome" complex, as well as recruitment of RIP to the receptor together with the three major signalosome components, NEMO, IKK1 and IKK2, and some kind of covalent modification of the recruited RIP molecules. It also induces binding of NEMO to the signaling inhibitor A20, and recruitment of A20 to the receptor. Enforced expression of NEMO in cells revealed that NEMO can both promote and block NF-kappaB activation and dramatically augments the phosphorylation of c-Jun. The findings suggest that the signaling activities of the **IKK** signalosome are regulated through **binding** of NEMO to RIP and A20 within the p55 TNF receptor complex.

L73 ANSWER 114 OF 150 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
 AB US 5916760 A UPAB: 19990928  
 NOVELTY - A method (I) of screening for agents which modulate the interaction of human **IKK**- beta polypeptides and their **binding** targets, is new. **IKK**- beta is a novel I $\kappa$ B Kinase (I-Kappa B-Kinase, one of a family of inhibitory proteins which interact with Nuclear Factor Kappa B (NF- $\kappa$ B), see Finco et al., (1995)) which interacts with NIK (Nuclear Factor-Kappa B-Inducing Kinase).  
 DETAILED DESCRIPTION - A method (I) of screening for an agent which modulates the interaction of an **IKK**- beta polypeptide to a **binding** target, which comprises:  
 (i) incubating a mixture (A) under conditions in which, but for the presence of the agent, the polypeptide specifically binds the binding target at a reference affinity (rA) ((A) comprises:  
 (1) a polypeptide comprising at least 31 consecutive residues of a

defined 756 residue amino acid sequence (X) given in the specification;

(2) a binding target of the polypeptide; and

(3) a candidate modulating agent); and

(ii) detecting the binding affinity of the polypeptide to the binding target to determine an agent-biased affinity (aA) (in which a difference between aA and rA indicates that the agent modulates the binding of the polypeptide to the binding target).

USE - (I) may be used to screen for agents which modulate the interaction of **IKK**- beta polypeptides and their **binding** targets. Agents which modulate the **IKK**- beta **binding** are useful in a variety of diagnostic and therapeutic applications where the disease is associated with improper utilization of a pathway involving IKK- beta proteins (e.g. NF-kB activation and IKK- beta -dependent transcriptional activation). Example IKK- beta Ikb Kinase inhibitors include known classes of serine/threonine Kinase (e.g. PKC (not defined)) inhibitors such as competitive inhibitors of ATP (adenine triphosphate) and substrate binding and antibiotics.

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L73 ANSWER 117 OF 150 MEDLINE on STN DUPLICATE 76  
AB Rap1 GTPase is activated by a variety of stimulations in many types of cells, but its exact functions remain unknown. In this study we have shown that **SPA-1** interferes with Rap1 activation by membrane-targeted C3G, C3G-F, in 293T cells through the GTPase activating protein (GAP) activity. **SPA-1** transiently expressed in HeLa cells was mostly localized at the cortical cytoskeleton and induced rounding up of the cells, whereas C3G-F conversely induced extensive cell spreading. Conditional **SPA-1** overexpression in HeLa cells by tetracycline-regulative system suppressed Rap1 activation upon plating on dishes coated with fibronectin and resulted in the reduced adhesion. When **SPA-1** was conditionally induced after the established cell adhesion, the cells gradually rounded up and detached from the dish. Both effects were counteracted by exogenous fibronectin in a dose-dependent manner. Retroviral overexpression of **SPA-1** in promyelocytic 32D cells also inhibited both activation of Rap1 and induction of cell adhesion by granulocyte colony stimulating factor without affecting differentiation. These results have indicated that Rap1 GTP is required for the cell adhesion induced by both extracellular matrix and soluble factors, which is negatively regulated by **SPA-1**.

L73 ANSWER 119 OF 150 MEDLINE on STN DUPLICATE 78  
AB The activation of NF-kappaB by receptors in the tumor necrosis factor (TNF) receptor and Toll/interleukin-1 (IL-1) receptor families requires the TRAF family of adaptor proteins. Receptor oligomerization causes the recruitment of TRAFs to the receptor complex, followed by the activation of a kinase cascade that results in the phosphorylation of IkappaB. TANK is a TRAF-binding protein that can inhibit the binding of TRAFs to receptor tails and can also inhibit NF-kappaB activation by these receptors. However, TANK also displays the ability to stimulate TRAF-mediated NF-kappaB activation. In this report, we investigate the mechanism of the stimulatory activity of TANK. We find that TANK interacts with TBK1 (TANK-**binding** kinase 1), a novel **IKK**-related kinase that can activate NF-kappaB in a kinase-dependent manner. TBK1, TANK and TRAF2 can form a ternary complex, and complex formation appears to be required for TBK1 activity. Kinase-inactive TBK1 inhibits TANK-mediated NF-kappaB activation but does not block the activation mediated by TNF-alpha, IL-1 or CD40. The TBK1-TANK-TRAF2 signaling complex functions upstream of NIK and the IKK complex and represents an alternative to the receptor signaling complex for TRAF-mediated activation of NF-kappaB.

L73 ANSWER 120 OF 150 MEDLINE on STN DUPLICATE 79  
AB Activation of the transcription factor NF-kappaB depends on the specific

dual phosphorylation of its inhibitor protein IkappaB by the homologous cytokine-inducible IkappaB kinases 1 and 2 (IKK1/2). Various IkappaB isoforms exist: IkappaBalpha, IkappaBbeta1/2 (two alternative splice variants), and IkappaBepsilon. However, the individual relevance and the specific regulation of these isoforms is not well-understood. We have studied the direct interaction of recombinant IkappaBalpha, IkappaBbeta1, IkappaBbeta2, and IkappaBepsilon with the recombinant homodimeric IKK2. Fluorescence-based active site titration revealed that each **IKK2** dimer contains two **binding** sites for IkappaB. By using surface plasmon resonance analysis, we found that all IkappaB proteins interact with the **IKK2** dimer following a noncooperative **binding** mechanism. Further, the four IkappaB proteins bind to the kinase with equilibrium dissociation constants (KD) in the range of 50-300 nM; the association rate constants for all IkappaB isoforms with IKK2 were between  $6.0 \times 10^3$  and  $22.5 \times 10^3$  M<sup>-1</sup> s<sup>-1</sup>, and the dissociation rate constants were between  $1.25 \times 10^{-3}$  and  $1.75 \times 10^{-3}$  s<sup>-1</sup>. This high-affinity binding suggests that the previously observed preassociation of all analyzed IkappaB proteins with the biochemically purified 700 kDa IkappaB kinase (IKK) complex is based on a direct enzyme-substrate association between the various IkappaB isoforms and the IKK proteins. The apparent catalytic efficiencies (kcat/KM) of IKK2 for IkappaBalpha, IkappaBbeta1, IkappaBbeta2, and IkappaBepsilon were  $22 \times 10^3$ ,  $10 \times 10^3$ ,  $5.4 \times 10^3$ , and  $8.5 \times 10^3$  s<sup>-1</sup> M<sup>-1</sup>, respectively, with KM values ranging between  $1.7 \times 10^{-6}$  and  $3.2 \times 10^{-6}$  M and kcat values ranging between  $1.5 \times 10^{-2}$  and  $3.7 \times 10^{-2}$  s<sup>-1</sup>. The relative affinities and catalytic efficiencies of IKK2 for the IkappaB isoforms were also reflected by the kinetics observed for the TNF-induced, phosphorylation-dependent degradation of the alpha, beta1, beta2, and epsilon isoforms of IkappaB in human umbilical vein endothelial cells. Therefore, differential regulation of the IkappaB isoforms in some cell types is not a direct result of the IKK activity, but appears to be due to parallel events.

L73 ANSWER 122 OF 150 MEDLINE on STN DUPLICATE 81  
 AB The atypical protein kinase C (PKC) isotypes (lambda/iotaPKC and zetaPKC) have been shown to be critically involved in important cell functions such as proliferation and survival. Previous studies have demonstrated that the atypical PKCs are stimulated by tumor necrosis factor alpha (TNF-alpha) and are required for the activation of NF-kappaB by this cytokine through a mechanism that most probably involves the phosphorylation of IkappaB. The inability of these PKC isotypes to directly phosphorylate IkappaB led to the hypothesis that zetaPKC may use a putative IkappaB kinase to functionally inactivate IkappaB. Recently several groups have molecularly characterized and cloned two IkappaB kinases (IKKalpha and IKKbeta) which phosphorylate the residues in the IkappaB molecule that serve to target it for ubiquitination and degradation. In this study we have addressed the possibility that different PKCs may control NF-kappaB through the activation of the IKKs. We report here that alphaPKC as well as the atypical PKCs **bind** to the **IKKs** in vitro and in vivo. In addition, overexpression of zetaPKC positively modulates IKKbeta activity but not that of IKKalpha, whereas the transfection of a zetaPKC dominant negative mutant severely impairs the activation of IKKbeta but not IKKalpha in TNF-alpha-stimulated cells. We also show that cell stimulation with phorbol 12-myristate 13-acetate activates IKKbeta, which is entirely dependent on the activity of alphaPKC but not that of the atypical isoforms. In contrast, the inhibition of alphaPKC does not affect the activation of IKKbeta by TNF-alpha. Interestingly, recombinant active zetaPKC and alphaPKC are able to stimulate in vitro the activity of IKKbeta but not that of IKKalpha. In addition, evidence is presented here that recombinant zetaPKC directly phosphorylates IKKbeta in vitro, involving Ser177 and Ser181. Collectively, these results demonstrate a critical role for the PKC isoforms in the NF-kappaB pathway at the level of IKKbeta activation and IkappaB degradation.

L73 ANSWER 123 OF 150 MEDLINE on STN DUPLICATE 82  
AB Activation of the transcription factor NF-kappaB is controlled by the sequential phosphorylation, ubiquitination, and degradation of its inhibitory subunit, IkappaB. We recently purified a large multiprotein complex, the IkappaB kinase (IKK) signalsome, which contains two regulated IkappaB kinases, IKK1 and IKK2, that can each phosphorylate IkappaBalpha and IkappaBbeta. The IKK signalsome contains several additional proteins presumably required for the regulation of the NFkappaB signal transduction cascade in vivo. In this report, we demonstrate reconstitution of IkappaB kinase activity in vitro by using purified recombinant IKK1 and IKK2. Recombinant IKK1 or IKK2 forms homo- or heterodimers, suggesting the possibility that similar IKK complexes exist in vivo. Indeed, in HeLa cells we identified two distinct IKK complexes, one containing IKK1-IKK2 heterodimers and the other containing IKK2 homodimers, which display differing levels of activation following tumor necrosis factor alpha stimulation. To better elucidate the nature of the IKK signalsome, we set out to identify IKK-associated proteins. To this end, we purified and cloned a novel component common to both complexes, named IKK-associated protein 1 (IKKAP1). In vitro, IKKAP1 associated specifically with IKK2 but not IKK1. Functional analyses revealed that **binding to IKK2** requires sequences contained within the N-terminal domain of IKKAP1. Mutant versions of IKKAP1, which either lack the N-terminal **IKK2-binding** domain or contain only the **IKK2-binding** domain, disrupt the NF-kappaB signal transduction pathway. IKKAP1 therefore appears to mediate an essential step of the NF-kappaB signal transduction cascade. Heterogeneity of IKK complexes in vivo may provide a mechanism for differential regulation of NF-kappaB activation.

L73 ANSWER 125 OF 150 MEDLINE on STN DUPLICATE 83  
AB The high-risk human papillomaviruses (HPVs) are associated with carcinomas of the cervix and other genital tumors. Previous studies have identified two viral oncoproteins, E6 and E7, which are expressed in the majority of HPV-associated carcinomas. The ability of high-risk HPV E6 protein to immortalize human mammary epithelial cells (MECs) has provided a single-gene model to study the mechanisms of E6-induced oncogenic transformation. In this system, the E6 protein targets the p53 tumor suppressor protein for degradation, and mutational analyses have shown that E6-induced degradation of p53 protein is required for MEC immortalization. However, the inability of most dominant-negative p53 mutants to induce efficient immortalization of MECs suggests the existence of additional targets of the HPV E6 oncoprotein. Using the yeast two-hybrid system, we have isolated a novel E6-**binding** protein. This polypeptide, designated E6TP1 (E6-targeted protein 1), exhibits high homology to GTPase-activating proteins for Rap, including **SPA-1**, tuberin, and Rap1GAP. The mRNA for E6TP1 is widely expressed in tissues and in vitro-cultured cell lines. The gene for E6TP1 localizes to chromosome 14q23.2-14q24.3 within a locus that has been shown to undergo loss of heterozygosity in malignant meningiomas. Importantly, E6TP1 is targeted for degradation by the high-risk but not the low-risk HPV E6 proteins both in vitro and in vivo. Furthermore, the immortalization-competent but not the immortalization-incompetent HPV16 E6 mutants target the E6TP1 protein for degradation. Our results identify a novel target for the E6 oncoprotein and provide a potential link between HPV E6 oncogenesis and alteration of a small G protein signaling pathway.

L73 ANSWER 134 OF 150 HCAPLUS COPYRIGHT 2003 ACS on STN  
AB The cDNA encoding **SPA-1** protein was isolated from a cDNA library of lymphocytic LFD-14 cell line and its amino acid sequence deduced. Expression of the cDNA in transgenic NIH3T3 cells and Escherichia coli was observed. The genomic DNA was also isolated using the cDNA-derived probes from a murine genomic library (EMBL3-Adult DBA/2J liver). **SPA-1** protein contains a RanGAP activity domain in its N-terminus. **SPA-1** is deemed associated with DNA replication and cell division since it is highly expressed after

S phase in lymphocytes. It may be used as an antitumor agent by inducing apoptosis in S phase.

L73 ANSWER 139 OF 150 MEDLINE on STN DUPLICATE 89  
AB The transcription factor NF-kappaB coordinates the activation of numerous genes in response to pathogens and pro-inflammatory cytokines, and is, therefore, vital in the development of acute and chronic inflammatory diseases. NF-kappaB is activated by phosphorylation of its inhibitory subunit, IkappaB-alpha, on serine residues 32 and 36 by cytokine-activated IKB kinases (IKKs); this phosphorylation precedes rapid degradation of IkappaB. IKK-alpha and IKK-beta isozymes are found in large complexes of relative molecular mass 700,000-900,000 (M(r) 70K-90K), but little is known about other components that organize and regulate these complexes. IKK-alpha was independently discovered as a NF-kappaB-inducing kinase (NIK)-associated protein in a yeast two-hybrid screen, and IKK-beta was also identified by homology screening. It is, however, unknown whether NIK is part of the IKK complex. Here we isolate large, interleukin-1-inducible IKK complexes that contain NIK, IKK-alpha, IKK-beta, IkappaB-alpha, NF-kappaB/RelA and a protein of M(r) 150K. This latter component is a new protein, termed IKK-complex-associated protein (IKAP), which can **bind** NIK and **IKKs** and assemble them into an active kinase complex. We show that IKAP is a scaffold protein and a regulator for three different kinases involved in pro-inflammatory cytokine signalling.

L73 ANSWER 143 OF 150 MEDLINE on STN DUPLICATE 91  
AB Mouse **Spa-1** gene with a region homologous to the human rap1GAP gene is transcriptionally induced in the lymphocytes by mitogenic stimulation. Herein we have cloned a cDNA for its human counterpart. **SPA-1** cDNA encodes a 130-kDa protein (p130(**SPA-1**)) consisting of proline-rich regions and rap1GAP-related domain followed by a coiled-coil stretch. Baculovirally expressed p130(**SPA-1**) exhibited GTPase-activating protein (GAP) activity for Rap1 and Rap2, but not for Ras, Rho, Cdc42, Rac, and Ran, with comparable specific activity to the rap1GAP gene product (p85/95(rap1GAP)). In the cells, p130(**SPA-1**) was mostly localized at the perinuclear membranous region co-localizing with Rap1 and Rap2. Expression of **SPA-1** and rap1GAP genes tended to be segregate in various tissues, lymphoid tissues expressing abundant **SPA-1** transcript without rap1GAP, while those such as brain, kidney, and pancreas exhibiting rap1GAP mRNA with little **SPA-1**. Promyelocytic HL-60 cells, which expressed p130(**SPA-1**) with little p85/95(rap1GAP) in uninduced state, showed progressive decline in p130(**SPA-1**) and conversely drastic increase in p85/95(rap1GAP) as they ceased from proliferation and differentiated into macrophages by 12-O-tetradecanoylphorbol-13-acetate. These results suggested that products of **SPA-1** and rap1GAP genes, albeit comparable GAP activity for Rap1 and Rap2, functioned in the distinct contexts depending on cell types and/or states.

L73 ANSWER 145 OF 150 MEDLINE on STN DUPLICATE 93  
AB The two Ras-related GTPases called Rap1 and Rsr1, which share 50% sequence identity with Ras GTPases are known to be activated by two distinct mammalian GAPs, i.e. cytosolic GAP3c of 55 kDa and membrane-bound GAP3m of 85 kDa. Recently we have cloned a gene encoding a 68 kDa (p68) protein product, which is associated with chromosomes during interphase. The N-terminal 190 amino acids share 43% sequence identity with the second half of the GTPase activating domain (residues 210-397) of GAP3m. The N-terminal fragment of 209 amino acids of **Spa-1** (called Span-N) was overproduced in E. coli as a glutathione S-transferase (GST) fusion protein and affinity purified. Rap1 and Rsr1 GTPase stimulatory activity of **Spa-1** was tested and compared with GAP3m. **Spa-1** preferentially stimulates Rsr1

GTPase rather than Rap1 GTPase, while GAP3m has a preference for Rap1 GTPase. This suggests that although **Spa-1** and GAP3m stimulate GTPase of Rap1 family members, they differ in affinity for them. By mutational analysis it was also found that amino acid residues 10-183 are enough for Rap GAP activity of **Spa-1**.

L73 ANSWER 146 OF 150 MEDLINE on STN DUPLICATE 94  
 AB We have cloned a novel cDNA (**Spa-1**) which is little expressed in the quiescent state but induced in the interleukin 2-stimulated cycling state of an interleukin 2-responsive murine lymphoid cell line by differential hybridization. **Spa-1** mRNA (3.5 kb) was induced in normal lymphocytes following various types of mitogenic stimulation. In normal organs it is preferentially expressed in both fetal and adult lymphohematopoietic tissues. A **Spa-1**-encoded protein of 68 kDa is localized mostly in the nucleus. Its N-terminal domain is highly homologous to a human Rap1 GTPase-activating protein (GAP), and a fusion protein of this domain (SpanN) indeed exhibited GAP activity for Rap1/Rsr1 but not for Ras or Rho in vitro. Unlike the human Rap1 GAP, however, SpanN also exhibited GAP activity for Ran, so far the only known Ras-related GTPase in the nucleus. In the presence of serum, stable **Spa-1** cDNA transfectants of NIH 3T3 cells (NIH/**Spa-1**) hardly overexpressed **Spa-1** (p68), and they grew as normally as did the parental cells. When NIH/**Spa-1** cells were serum starved to be arrested in the G1/G0 phase of the cell cycle, however, they, unlike the control cells, exhibited progressive **Spa-1** p68 accumulation, and following the addition of serum they showed cell death resembling mitotic catastrophes of the S phase during cell cycle progression. The results indicate that the novel nuclear protein **Spa-1**, with a potentially active Ran GAP domain, severely hampers the mitogen-induced cell cycle progression when abnormally and/or prematurely expressed. Functions of the **Spa-1** protein and its regulation are discussed in the context of its possible interaction with the Ran/RCC-1 system, which is involved in the coordinated nuclear functions, including cell division.

=> log y		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	45.25	45.46
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-5.86	-5.86

STN INTERNATIONAL LOGOFF AT 13:08:50 ON 05 NOV 2003

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 10:19:54 ON 10 NOV 2003

=> fil .bec		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS, ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 10:20:08 ON 10 NOV 2003  
 ALL COPYRIGHTS AND RESTRICTIONS APPLY. SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

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FILE 'MEDLINE'
    10003 RAP#
    28798 GAP
    7296 GTPASE
    51438 ACTIVATING
    1548288 PROTEIN#
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    49608 ACTIVATING
    1238832 PROTEIN#
    2649 GTPASE ACTIVATING PROTEIN#
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L2      137 RAP# AND (GAP OR GTPASE ACTIVATING PROTEIN#)

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    852 GTPASE ACTIVATING PROTEIN#
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    157455 GAP

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FILE 'NTIS'

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              40 GTPASE
              865 ACTIVATING
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FILE 'ESBIOBASE'

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          4758 GTPASE
          21145 ACTIVATING
553333 PROTEIN#
          1129 GTPASE ACTIVATING PROTEIN#
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FILE 'BIOTECHNO'

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          4051 GTPASE
          20402 ACTIVATING
636572 PROTEIN#
          1154 GTPASE ACTIVATING PROTEIN#
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FILE 'WPIDS'

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              145 GTPASE
          38918 ACTIVATING
118158 PROTEIN#
          32 GTPASE ACTIVATING PROTEIN#
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L11         19 RAP# AND (GAP OR GTPASE ACTIVATING PROTEIN#)

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TOTAL FOR ALL FILES

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L12         931 RAP# AND (GAP OR GTPASE ACTIVATING PROTEIN#)

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=> s l12 and ikk?

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FILE 'SCISEARCH'

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FILE 'LIFESCI'

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          384 IKK?
L15         0 L3 AND IKK?

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FILE 'BIOTECHDS'

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      43 IKK?
L16      0 L4 AND IKK?

FILE 'BIOSIS'
      889 IKK?
L17      0 L5 AND IKK?

FILE 'EMBASE'
      625 IKK?
L18      0 L6 AND IKK?

FILE 'HCAPLUS'
      926 IKK?
L19      0 L7 AND IKK?

FILE 'NTIS'
      37 IKK?
L20      0 L8 AND IKK?

FILE 'ESBIOBASE'
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L21      0 L9 AND IKK?

FILE 'BIOTECHNO'
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L22      0 L10 AND IKK?

FILE 'WPIDS'
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L23      0 L11 AND IKK?

TOTAL FOR ALL FILES
L24      0 L12 AND IKK?

=> s tank
FILE 'MEDLINE'
L25      2661 TANK

FILE 'SCISEARCH'
L26      14378 TANK

FILE 'LIFESCI'
L27      2956 TANK

FILE 'BIOTECHDS'
L28      4677 TANK

FILE 'BIOSIS'
L29      9134 TANK

FILE 'EMBASE'
L30      4844 TANK

FILE 'HCAPLUS'
L31      89425 TANK

FILE 'NTIS'
L32      17529 TANK

FILE 'ESBIOBASE'
L33      2880 TANK

FILE 'BIOTECHNO'
L34      2791 TANK

```

FILE 'WPIDS'  
L35 220231 TANK

TOTAL FOR ALL FILES  
L36 371506 TANK

=> s l36 and ikk?

FILE 'MEDLINE'  
1796 IKK?  
L37 10 L25 AND IKK?

FILE 'SCISEARCH'  
965 IKK?  
L38 8 L26 AND IKK?

FILE 'LIFESCI'  
384 IKK?  
L39 4 L27 AND IKK?

FILE 'BIOTECHDS'  
43 IKK?  
L40 0 L28 AND IKK?

FILE 'BIOSIS'  
889 IKK?  
L41 9 L29 AND IKK?

FILE 'EMBASE'  
625 IKK?  
L42 8 L30 AND IKK?

FILE 'HCAPLUS'  
926 IKK?  
L43 7 L31 AND IKK?

FILE 'NTIS'  
37 IKK?  
L44 0 L32 AND IKK?

FILE 'ESBIOBASE'  
564 IKK?  
L45 4 L33 AND IKK?

FILE 'BIOTECHNO'  
432 IKK?  
L46 6 L34 AND IKK?

FILE 'WPIDS'  
90 IKK?  
L47 1 L35 AND IKK?

TOTAL FOR ALL FILES  
L48 57 L36 AND IKK?

=> dup rem l48

PROCESSING COMPLETED FOR L48

L49 16 DUP REM L48 (41 DUPLICATES REMOVED)

=> d tot

L49 ANSWER 1 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New tricyclic compounds are I-kappa B kinase inhibitors used for treating  
e.g. inflammation and cancer.

PI WO 2003070706 A1 20030828 (200368)\* EN 61p C07D231-54  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS  
 LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
 ZM ZW  
 IN CLARE, M; LENNON, P; METZ, S; VAZQUEZ, M; WEIER, R M; WOLFSON, S G; XU, X  
  
 L49 ANSWER 2 OF 16 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN  
 TI Toll/IL-1 receptor domain-containing adaptor inducing IFN-beta (TRIF)  
 associates with TNF receptor-associated factor 6 and **TANK**  
 -Binding kinase 1, and activates two distinct transcription factors,  
 NF-kappa B and IFN-regulatory factor-3, in the toll-like receptor  
 signaling  
 SO JOURNAL OF IMMUNOLOGY, (15 OCT 2003) Vol. 171, No. 8, pp. 4304-4310.  
 Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD  
 20814 USA.  
 ISSN: 0022-1767.  
 AU Sato S; Sugiyama M; Yamamoto M; Watanabe Y; Kawai T; Takeda K; Akira S  
 (Reprint)  
 AN 2003:890040 SCISEARCH  
  
 L49 ANSWER 3 OF 16 MEDLINE on STN DUPLICATE 1  
 TI Triggering the interferon antiviral response through an **IKK**  
 -related pathway.  
 SO SCIENCE, (2003 May 16) 300 (5622) 1148-51.  
 Journal code: 0404511. ISSN: 1095-9203.  
 AU Sharma Sonia; tenOever Benjamin R; Grandvaux Nathalie; Zhou Guo-Ping; Lin  
 Rongtuan; Hiscott John  
 AN 2003228927 MEDLINE  
  
 L49 ANSWER 4 OF 16 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN  
 TI Triggering the interferon antiviral response through an **IKK**  
 -related pathway  
 SO SCIENCE, (16 MAY 2003) Vol. 300, No. 5622, pp. 1148-1151.  
 Publisher: AMER ASSOC ADVANCEMENT SCIENCE, 1200 NEW YORK AVE, NW,  
 WASHINGTON, DC 20005 USA.  
 ISSN: 0036-8075.  
 AU Sharma S; tenOever B R; Grandvaux N; Zhou G P; Lin R T (Reprint); Hiscott  
 J  
 AN 2003:395225 SCISEARCH  
  
 L49 ANSWER 5 OF 16 MEDLINE on STN DUPLICATE 2  
 TI **IKKepsilon** and TBK1 are essential components of the IRF3  
 signaling pathway.  
 SO Nat Immunol, (2003 May) 4 (5) 491-6.  
 Journal code: 100941354. ISSN: 1529-2908.  
 AU Fitzgerald Katherine A; McWhirter Sarah M; Faia Kerrie L; Rowe Daniel C;  
 Latz Eicke; Golenbock Douglas T; Coyle Anthony J; Liao Sha-Mei; Maniatis  
 Tom  
 AN 2003199991 MEDLINE  
  
 L49 ANSWER 6 OF 16 MEDLINE on STN  
 TI Genomic structure and characterization of the promoter region of the human  
 NAK gene.  
 SO GENE, (2003 Jan 30) 304 57-64.  
 Journal code: 7706761. ISSN: 0378-1119.  
 AU Li Sheng Fan; Fujita Fumitaka; Hirai Momoki; Lu Rui; Niida Hiroyuki;  
 Nakanishi Makoto  
 AN 2003058678 MEDLINE  
  
 L49 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 3

TI Association of the adaptor **TANK** with the I kappa B kinase (**IKK**) regulator NEMO connects **IKK** complexes with **IKK** epsilon and TBK1 kinases.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Oct 4) 277 (40) 37029-36.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 AU Chariot Alain; Leonardi Antonio; Muller Jurgen; Bonif Marianne; Brown Keith; Siebenlist Ulrich  
 AN 2002493273 MEDLINE

L49 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 4  
 TI **IKK**-i and TBK-1 are enzymatically distinct from the homologous enzyme **IKK**-2: comparative analysis of recombinant human **IKK**-i, TBK-1, and **IKK**-2.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Apr 19) 277 (16) 13840-7.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 AU Kishore Nandini; Huynh Q Khai; Mathialagan Sumathy; Hall Troii; Rouw Sharon; Creely David; Lange Gary; Carroll James; Reitz Beverley; Donnelly Ann; Boddupalli Hymavathi; Combs Rodney G; Kretzmer Kuniko; Tripp Catherine S  
 AN 2002217150 MEDLINE

L49 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
 TI Kinetic mechanisms of IkappaB-related kinases (**IKK**) inducible **IKK** and TBK-1 differ from **IKK**-1/**IKK**-2 heterodimer.  
 SO Journal of Biological Chemistry, (April 12, 2002) Vol. 277, No. 15, pp. 12550-12558. print.  
 CODEN: JBCHA3. ISSN: 0021-9258.  
 AU Huynh, Q. Khai [Reprint author]; Kishore, Nandini; Mathialagan, Sumathy; Donnelly, Ann M.; Tripp, Catherine S.  
 AN 2002:287067 BIOSIS

L49 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 5  
 TI Expression of different NF-kappaB pathway genes in dendritic cells (DCs) or macrophages assessed by gene expression profiling.  
 SO JOURNAL OF CELLULAR BIOCHEMISTRY, (2001 Aug 1-9) 83 (2) 281-90.  
 Journal code: 8205768. ISSN: 0730-2312.  
 AU Baltathakis I; Alcantara O; Boldt D H  
 AN 2001525607 MEDLINE

L49 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 6  
 TI The NF-kappaB pathway in human endometrium and first trimester decidua.  
 SO MOLECULAR HUMAN REPRODUCTION, (2001 Feb) 7 (2) 175-83.  
 Journal code: 9513710. ISSN: 1360-9947.  
 AU King A E; Critchley H O; Kelly R W  
 AN 2001225756 MEDLINE

L49 ANSWER 12 OF 16 MEDLINE on STN  
 TI A new family of **IKK**-related kinases may function as I kappa B kinase kinases.  
 SO BIOCHIMICA ET BIOPHYSICA ACTA, (2001) 1471 (2) M57-62. Ref: 29  
 Journal code: 0217513. ISSN: 0006-3002.  
 AU Peters R T; Maniatis T  
 AN 2001259016 MEDLINE

L49 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
 TI Molecular cloning and characterization of a novel **IKK**-kinase (NAK) binding protein (NAKBP) which inhibits NF-kappaB activation.  
 SO Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.497. print.  
 Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal

Endoscopy; Society for Surgery of the Alimentary Tract.  
CODEN: GASTAB. ISSN: 0016-5085.

AU Fujita, Fumitaka [Reprint author]; Joh, Takashi; Seno, Kyoji [Reprint author]; Matsui, Taido [Reprint author]; Okumura, Fuminori [Reprint author]; Kataoka, Hiromi [Reprint author]; Sasaki, Makoto [Reprint author]; Ohshima, Tadayuki [Reprint author]; Takezono, Yasuhide [Reprint author]; Yokoyama, Yoshifumi [Reprint author]; Itoh, Makoto [Reprint author]; Nakanishi, Makoto [Reprint author]  
AN 2002:201052 BIOSIS

L49 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI Chronic lymphocytic leukemia B cells impair immunoglobulin class switching by dysregulating a CD30+ T cell-dependent CD40-inhibitory pathway.  
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 472a. print.  
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.  
CODEN: BLOOAW. ISSN: 0006-4971.  
AU Cerutti, Andrea [Reprint author]; Schaffer, Andras [Reprint author]; Casali, Paolo [Reprint author]  
AN 2001:332906 BIOSIS

L49 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 7  
TI NF-kappaB activation through **IKK**-i-dependent I-TRAF/**TANK** phosphorylation.  
SO GENES TO CELLS, (2000 Mar) 5 (3) 191-202.  
Journal code: 9607379. ISSN: 1356-9597.  
AU Nomura F; Kawai T; Nakanishi K; Akira S  
AN 2000223869 MEDLINE

L49 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 8  
TI NF-kappaB activation by a signaling complex containing TRAF2, **TANK** and TBK1, a novel **IKK**-related kinase.  
SO EMBO JOURNAL, (1999 Dec 1) 18 (23) 6694-704.  
Journal code: 8208664. ISSN: 0261-4189.  
AU Pomerantz J L; Baltimore D  
AN 2000050564 MEDLINE

=> d ab tot

L49 ANSWER 1 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
AB WO2003070706 A UPAB: 20031022  
NOVELTY - Tricyclic compounds (I) are new.  
DETAILED DESCRIPTION - Tricyclic compounds of formula (I), their isomers, tautomers, esters, prodrugs and salts, are new.  
A = (CH<sub>2</sub>)<sub>m</sub> (optionally substituted by at least one OH, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl or alkynyl);  
m = 0-8;  
Q = 5- or 6-membered heteroaryl, or aryl (optionally substituted by R<sub>1</sub>, R<sub>2</sub> or R<sub>12</sub>);  
B' = aromatic heterocyclyl;  
X = N or C;  
Y, Z = N, C, CH, CR<sub>3</sub>, S or O;  
R<sub>1</sub> = aryl, heteroaryl, alkenyl, alkynyl, alkyl, haloalkyl or OR<sub>5</sub> (all optionally substituted by T<sub>1</sub>, hydroxyalkyl, aryl, heteroaryl, alkyl, haloalkyl, COCF<sub>3</sub> or OR<sub>5</sub>), H or T<sub>1</sub>;  
T<sub>1</sub> = halo, CN, NO<sub>2</sub>, OCOOR<sub>5</sub>, CO<sub>2</sub>R<sub>7</sub>, CON(R<sub>6</sub>)R<sub>7</sub>, COR<sub>6</sub>, SR<sub>6</sub>, SOR<sub>6</sub>, SO<sub>2</sub>R<sub>6</sub>, NR<sub>6</sub>R<sub>7</sub>, NR<sub>6</sub>COR<sub>7</sub>, NR<sub>6</sub>CONHR<sub>7</sub>, NR<sub>6</sub>SO<sub>2</sub>R<sub>7</sub>, NR<sub>6</sub>SO<sub>2</sub>NHR<sub>7</sub> or SO<sub>2</sub>N(R<sub>6</sub>)R<sub>7</sub>;  
R<sub>6</sub>, R<sub>7</sub> = H, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclylalkyl or heterocyclyl, or  
R<sub>6</sub> + R<sub>7</sub> = 3-7 membered carbocyclyl containing 1-3 optionally substituted S, SO, SO<sub>2</sub>, O or NR<sub>6</sub> heteroatoms;

R2 = halo, H, hydroxyalkyl, OR6, CN, NO2, SR6, NHR6, CON(R6)R7, NHCONHR6, CO2H, alkyl or haloalkyl, or

R1 + R2 = 5-7 membered carbocyclyl optionally containing 1-3 N, O or S heteroatoms (optionally substituted by R1);

R3 = optionally substituted amidine, alkylamino, aminoalkyl, CONHR16, NH2, NHCOR6 or CH2NHCOR6;

R4 = heterocyclyl, aryl, heteroaryl or alkenyl (all optionally substituted by R9), halo, alkylsulfinyl, alkylsulfonyl, CN, alkoxy carbonyl, alkyl, haloalkyl, H, hydroxyalkyl, haloalkoxy, NO2, acylamino, OR13, SR8, SO2N(R8)R8a, NHR9, NHCOR9, NR9COR9, NHCO(OR9), NR9CO(OR9), NR8SO2R10, NHCO2N(R10)R10a, NR6CON(R10)R10a, COR9, CO2R8 or CON(R8)R8a;

R5, R13 = alkyl, aryl, heteroaryl, heterocyclylalkyl, arylalkyl or heteroarylalkyl (all optionally substituted by at least one OR14, N(R14)R14a or glycols) or H;

R8, R8a = H, aryl, heteroaryl, heterocyclyl, alkyl, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl or heterocyclylalkyl, or

R8+R8a = 3-7 membered carbocyclyl containing 1-3 optionally substituted S, SO, SO2, O, N or NR6 heteroatoms;

R9 = aminoalkyl, lower alkyl, aryl, heteroaryl or arylalkyl (all optionally substituted by T2), heterocyclyl, cycloalkyl, heterocyclylalkyl, haloalkyl, H, arylalkylamino, amino, aminoacyl, nitro, azido or heteroarylalkyl;

T2 = alkylsulfonamide, sulfamyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, halo, acyloxy, oxy, formyl, alkyl, haloalkyl, CN, alkoxy, haloalkoxy, acyl, carboxyl, OH, hydroxyalkyloxy, phenoxy, NO2, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkylidioxy, hydroxyalkyl, alkylamino, alkylalkoxy carbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy or heterocyclyl (optionally substituted by alkyl, alkylamino, aminoalkyl, hydroxyalkyl or alkylaminoalkyl);

R10, R10a = arylalkyl, aryl, heteroaryl or heterocyclyl (all optionally substituted by at least one T3), haloalkyl, arylalkylamino, heteroarylalkyl, H or lower alkyl, or

R10 + R10a = 3-7 membered carbocyclyl containing 1-3 optionally substituted S, SO, SO2, O, N or NR6 heteroatoms;

T3 = halo, alkyl, haloalkyl, CN, alkoxy, haloalkoxy, acyl, carboxyl, OH, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, or heterocyclyl;

R11 = H, halo, haloalkyl, CN, CO2R5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy or CONH2;

R12 = H, halo, alkyl or alkoxy;

R14, R14a = H or lower alkyl;

R15 = aryl or arylalkyl (both optionally substituted by at least one of T5), H, halo, cycloalkyl, alkyl, haloalkyl, heteroaryl, heterocyclyl, alkylalkene, alkylalkyne, OH, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, NO2, CN, alkylthio, alkylsulfinyl or alkylsulfonyl;

T5 = halo, alkyl, haloalkyl, CN, alkoxy, haloalkoxy, acyl, carboxy, OH, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy or heterocyclyl, and

R16 = H, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy or alkoxyalkyl.

ACTIVITY - Cytostatic; Antiinflammatory; Antiarthritic; Analgesic; Antipyretic.

MECHANISM OF ACTION - I-kappa B (IKK) kinase inhibitor; IKK1 inhibitor; IKK2 inhibitor; IKK alpha /IKK beta heterodimer inhibitor; TANK-binding kinase inhibitor; IKKi inhibitor; Protein kinase C inhibitor; Cyclin dependent kinase inhibitor.

In an IKK heterodimer resin enzyme assay using a biotinylated IkB alpha peptide, results showed that 1-(4-(aminosulfonyl)phenyl)-1,4,5,6-tetrahydropyrazolo(3,4-e)indazole-3-carboxamide (Ia) exhibited an LC50

value of 0.67  $\mu$  M for inhibiting IKK.

USE - Used for treating cancer, inflammation, and inflammation associated disorders, particularly arthritis, pain and fever (all claimed).  
Dwg.0/0

L49 ANSWER 2 OF 16 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB We previously reported a new Toll/IL-1R (TIR)-containing molecule, named TIR domain-containing adaptor inducing IFN-beta (TRIF). Although initial study indicated that TRIF possesses the ability to activate not only the NF-kappaB-dependent but also the IFN-beta promoters, the molecular mechanisms of TRIF-induced signaling are poorly understood. In this study, we investigated the signaling cascades through TRIF. TNF receptor-associated factor (TRAF)6 interacted with TRIF through the TRAF domain of TRAF6 and TRAF6-binding motifs found in the N-terminal portion of TRIF. Disruption of TRAF6-binding motifs of TRIF disabled it from associating with TRAF6, and resulted in a reduction in the TRIF-induced activation of the NF-kappaB-dependent but not IFN-beta promoter. **TANK**-binding kinase (TBK)-1, which was recently reported to be a kinase of IFN regulatory factor-3, which is an essential transcription factor for IFN-beta expression, also associated with the N-terminal region of TRIF. Moreover, the association between TRIF and TBK1 appeared to require the kinase activity of TBK1, as well as phosphorylation of TRIF. Because TRAF6 and TBK1 bind close the region of TRIF, it seems that TRAF6 physically prevents the association between TRIF and TBK1. Taken together, these results demonstrate that TRIF associates with TRAF6 and TBK1 independently, and activates two distinct transcription factors, NF-kappaB and IFN regulatory factor-3, respectively.

L49 ANSWER 3 OF 16 MEDLINE on STN DUPLICATE 1

AB Rapid induction of type I interferon expression, a central event in establishing the innate antiviral response, requires cooperative activation of numerous transcription factors. Although signaling pathways that activate the transcription factors nuclear factor kappaB and ATF-2/c-Jun have been well characterized, activation of the interferon regulatory factors IRF-3 and IRF-7 has remained a critical missing link in understanding interferon signaling. We report here that the IkappaB kinase (**IKK**)-related kinases **IKKepsilon** and **TANK**-binding kinase 1 are components of the virus-activated kinase that phosphorylate IRF-3 and IRF-7. These studies illustrate an essential role for an **IKK**-related kinase pathway in triggering the host antiviral response to viral infection.

L49 ANSWER 4 OF 16 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB Rapid induction of type I interferon expression, a central event in establishing the innate antiviral response, requires cooperative activation of numerous transcription factors. Although signaling pathways that activate the transcription factors nuclear factor kappaB and ATF-2/c-Jun have been well characterized, activation of the interferon regulatory factors IRF-3 and IRF-7 has remained a critical missing link in understanding interferon signaling. We report here that the IkappaB kinase (**IKK**)-related kinases **IKKepsilon** and **TANK**-binding kinase 1 are components of the virus-activated kinase that phosphorylate IRF-3 and IRF-7. These studies illustrate an essential role for an **IKK**-related kinase pathway in triggering the host antiviral response to viral infection.

L49 ANSWER 5 OF 16 MEDLINE on STN DUPLICATE 2

AB The transcription factors interferon regulatory factor 3 (IRF3) and NF-kappaB are required for the expression of many genes involved in the innate immune response. Viral infection, or the binding of double-stranded RNA to Toll-like receptor 3, results in the coordinate activation of IRF3 and NF-kappaB. Activation of IRF3 requires signal-dependent phosphorylation, but little is known about the signaling

pathway or kinases involved. Here we report that the noncanonical IkappaB kinase homologs, IkappaB kinase-epsilon (**IKKepsilon**) and **TANK**-binding kinase-1 (TBK1), which were previously implicated in NF-kappaB activation, are also essential components of the IRF3 signaling pathway. Thus, **IKKepsilon** and TBK1 have a pivotal role in coordinating the activation of IRF3 and NF-kappaB in the innate immune response.

L49 ANSWER 6 OF 16 MEDLINE on STN

AB NAK has been identified as an IkappaB-kinase activating-kinase that plays an important role in NF-kappaB activation in response to several pro-inflammatory cytokines such as TNF-alpha. We describe here the genomic structure of the human NAK gene and analysis of the promoter. The gene spanned 40.5 kb and contained 21 exons with lengths ranging from 39 to 196 bp. Comparison of the phase and position of intron insertions within the human NAK gene with those within **IKKalpha**, **IKKbeta** and **IKK epsilon** indicated that the exon/intron organization of **IKK epsilon** is more highly conserved than that of **IKKalpha** or **IKKbeta**. The transcriptional start site was mapped at a position about 98 bp upstream from the translation start site by means of both an RNase protection assay and a primer extension method. Fluorescence in situ hybridization using full-length human NAK cDNA as a probe showed that the human NAK gene is localized to human chromosome 13q14.2-3, a region in which the loss of heterozygosity is associated with squamous cell carcinoma and leukemia. By using a series of deletion constructs in performing a reporter assay, a minimal 77 bp upstream of the transcriptional initiation site was shown to contribute to the major promoter activity.

L49 ANSWER 7 OF 16 MEDLINE on STN

DUPLICATE 3

AB Canonical activation of NF-kappa B is mediated via phosphorylation of the inhibitory I kappa B proteins by the I kappa B kinase complex (**IKK**). **IKK** is composed of a heterodimer of the catalytic **IKK alpha** and **IKK beta** subunits and a presumed regulatory protein termed NEMO (NF-kappa B essential modulator) or **IKK gamma**. NEMO/**IKK gamma** is indispensable for activation of the **IKKs** in response to many signals, but its mechanism of action remains unclear. Here we identify **TANK** (TRAF family member-associated NF-kappa B activator) as a NEMO/**IKK gamma**-interacting protein via yeast two-hybrid analyses. This interaction is confirmed in mammalian cells, and the domains required are mapped. **TANK** was previously shown to assist NF-kappa B activation in a complex with **TANK**-binding kinase 1 (TBK1) or **IKK epsilon**, two kinases distantly related to **IKK alpha/beta**, but the underlying mechanisms remained unknown. Here we show that TBK1 and **IKK epsilon** synergize with **TANK** to promote interaction with the **IKKs**. The **TANK** binding domain within NEMO/**IKK gamma** is required for proper functioning of this **IKK** subunit. These results indicate that **TANK** can synergize with **IKK epsilon** or TBK1 to link them to **IKK** complexes, where the two kinases may modulate aspects of NF-kappa B activation.

L49 ANSWER 8 OF 16 MEDLINE on STN

DUPLICATE 4

AB NF-kappaB is sequestered in the cytoplasm by the inhibitory IkappaB proteins. Stimulation of cells by agonists leads to the rapid phosphorylation of IkappaBs leading to their degradation that results in NF-kappaB activation. **IKK-1** and **IKK-2** are two direct IkappaB kinases. Two recently identified novel **IKKs** are **IKK-i** and TBK-1. We have cloned, expressed, and purified to homogeneity recombinant human (rh)**IKK-i** and rhTBK-1 and compared their enzymatic properties with those of rh**IKK-2**. We show that rh**IKK-i** and rhTBK-1 are enzymatically similar to each other. We demonstrate by phosphopeptide mapping and site-specific mutagenesis that rh**IKK-i** and rhTBK-1 are phosphorylated on serine 172 in the mitogen-activated protein

kinase kinase activation loop and that this phosphorylation is necessary for kinase activity. Also, rhIKK-i and rhTBK-1 have differential peptide substrate specificities compared with rhIKK-2, the mitogen-activated protein kinase kinase activation loop of **IKK**-2 being a more favorable substrate than the IkappaBalpha peptide. Finally, using analogs of ATP, we demonstrate unique differences in the ATP-binding sites of rhIKK-i, rhTBK-1, and rhIKK-2. Thus, although these **IKKs** are structurally similar, their enzymatic properties may provide insights into their unique functions.

L49 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
 AB Nuclear factor-kappaB activation depends on phosphorylation and degradation of its inhibitor protein, IkappaB. The phosphorylation of IkappaBalpha on Ser32 and Ser36 is initiated by an IkappaB kinase ( **IKK**) complex that includes a catalytic heterodimer composed of IkappaB kinase 1 (**IKK**-1) and IkappaB kinase 2 (**IKK**-2) as well as a regulatory adaptor subunit, NF-kappaB essential modulator. Recently, two related IkappaB kinases, TBK-1 and **IKK**-i, have been described. TBK-1 and **IKK**-i show sequence and structural homology to **IKK**-1 and **IKK**-2. TBK-1 and **IKK**-i phosphorylate Ser36 of IkappaBalpha. We describe the kinetic mechanisms in terms of substrate and product inhibition of the recombinant human (rh) proteins, rhTBK-1, rhIKK-1, and rhIKK-1/rhIKK-2 heterodimers. The results indicate that although each of these enzymes exhibits a random sequential kinetic mechanism, the effect of the binding of one substrate on the affinity of the other substrate is significantly different. ATP has no effect on the binding of an IkappaBalpha peptide for the rhIKK-1/rhIKK-2 heterodimer ( $\alpha=0.99$ ), whereas the binding of ATP decreased the affinity of the IkappaBalpha peptide for both rhTBK-1 ( $\alpha=10.16$ ) and rhIKK-i ( $\alpha=62.28$ ). Furthermore, the dissociation constants of ATP for rhTBK-1 and rhIKK-i are between the expected values for kinases, whereas the dissociation constants of the IkappaBalpha peptide for each **IKK** isoforms is unique with rhTBK-1 being the highest ( $K_{ikappaBalpha}=69.87 \mu M$ ), followed by rhIKK-i ( $K_{ikappaBalpha}=5.47 \mu M$ ) and rhIKK-1/rhIKK-2 heterodimers ( $K_{ikappaBalpha}=0.12 \mu M$ ). Thus this family of IkappaB kinases has very unique kinetic properties.

L49 ANSWER 10 OF 16 MEDLINE on STN DUPLICATE 5  
 AB NF-kappaB/Rel transcription factors have been implicated in the differentiation of monocytes to either dendritic cells (DCs) or macrophages, as well as in the maturation of DCs from antigen-processing to antigen-presenting cells. Recent studies of the expression pattern of Rel proteins and their inhibitors (IkappaBs) suggest that their regulation during this differentiation process is transcriptional. To investigate differential gene expression between macrophages and DCs, we used commercially available gene microarrays (GEArray KIT), which included four of the NF-kappaB/Rel family genes (p50/p105, p52/p100, RelB, and c-rel) and 32 additional genes either in the NF-kappaB signal transduction pathway or under transcriptional control of NF-kappaB/Rel factors. To generate macrophages and DCs, human adherent peripheral blood monocytes were cultured with M-CSF or GM-CSF + IL-4 respectively for up to 8 days. DCs (and in some experiments, macrophages) were treated with lipopolysaccharide (LPS) for the last 48 h of culture to induce maturation. Cells were harvested after 7 days, cDNA was prepared and radiolabeled with alpha-(32)P-dCTP, then hybridized to gene arrays containing specific gene probes. beta-actin and GAPDH or PUC18 oligonucleotides served as positive or negative controls, respectively. The expression of all four NF-kappaB/Rel family genes examined was significantly upregulated in maturing DCs compared to macrophages. The strongest difference was observed for c-rel. RT-PCR determinations of c-rel, RelB, and p105 mRNAs confirmed these observations. Among the 32 NF-kappaB/Rel pathway genes, 14 were upregulated in mature DCs compared to macrophages. These genes were IkappaBalpha, **IKK**-beta, NIK, ICAM-1, P-selectin, E-selectin, TNF-alpha, TNFR2, TNFAIP3, IL-1alpha,

IL-1R1, IL-1R2, IRAK, and **TANK**. By contrast, only mcp-1 (monocyte chemotactic protein 1) was upregulated in macrophages compared to DCs. NF-kappaB pathway genes upregulated in DCs compared to macrophages were constitutively expressed in monocytes then selectively downregulated during macrophage but not DC differentiation. LPS did not induce expression of most of these genes in macrophages but LPS did induce upregulation of IL-8 in mature macrophages. We conclude that NF-kappaB/Rel family genes, especially c-rel, are selectively expressed during differentiation of monocytes towards DCs. Moreover, this differential expression is associated both with activation of different NF-kappaB signal transduction pathways in DCs and macrophages and with expression of a unique subset of genes in DCs that are transcriptionally targeted by NF-kappaB/Rel factors. The results illustrate the ability of the NF-kappaB pathway to respond to differentiation stimuli by activating in a cell-specific manner unique signalling pathways and subsets of NF-kappaB target genes.

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- L49 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 6  
 AB Nuclear factor kappa B (NF-kappaB) regulates proinflammatory genes and may be involved in inflammation associated with reproductive events e.g. menstruation, implantation. Activation of NF-kappaB involves several protein kinases and subsequent degradation of an endogenous inhibitor, IkappaBalpha. This study details expression of NF-kappaB pathway intermediates in human endometrium and first trimester decidua. Messenger RNA was detected for IkappaBalpha, and IkappaB kinase gamma ( **IKKgamma**, a scaffolding protein) and the protein kinases, **IKKalpha**, **IKKbeta**, NF-kappaB inducing kinase (NIK), mitogen-activated protein kinase Erk kinase kinase 1 (MEKK1) and **TANK**-binding kinase 1 (TBK1) using real-time quantitative polymerase chain reaction (PCR). IkappaBalpha and TBK1 mRNA were increased in the perimenstrual phase of the menstrual cycle. This suggests that there is activation of NF-kappaB due to premenstrual progesterone withdrawal, since NF-kappaB activity increases IkappaBalpha gene expression. Differential expression of NF-kappaB pathway intermediates occurred when progesterone concentrations increased in early pregnancy; **IKKalpha** and NIK mRNA levels increased in decidua whilst **IKKbeta** and MEKK1 mRNA levels declined. Expression profiles of **IKKalpha** and NIK proteins were determined immunohistochemically. Both were detected in glandular epithelium and endothelium of endometrium. In decidua, both were present in epithelium and decidualized stromal cells. The results of this study suggest that NF-kappaB is activated during menstruation. During early pregnancy, NF-kappaB may also be activated (via **IKKalpha**-NIK) and may regulate the expression of molecules vital for implantation and successful pregnancy. However, pro-inflammatory signalling to NF-kappaB (via **IKKbeta**-MEKK1) may be down-regulated in early pregnancy, contributing to the immunosuppressive mechanisms which prevail at this time.

L49 ANSWER 12 OF 16 MEDLINE on STN

L49 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

- L49 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
 AB Chronic lymphocytic leukemia (CLL) is a B cell lymphoproliferative disorder associated with impaired Ig class switching from IgM to IgG and IgA, a defect that leads to recurrent bacterial infections. The pathogenesis of this immunodeficiency is poorly understood. Naive B cells undergo class switching upon engagement of CD40 by CD154 (CD40 ligand), a molecule expressed by T cells few hours after activation by antigen. A few days later, T cells express CD30, a physiological negative modulator of the immune response. We show here that, in CLL patients, CD8+ CD28-suppressor T cells are increased and constitutively express CD30. In

addition, leukemic CLL B cells rapidly up-regulate CD30 on CD4+ T cells through a CD134L (OX40 ligand) and IL-4-dependent mechanism. These leukemia-induced CD30+ T cells inhibit class switch DNA recombination (CSR) by engaging CD153 (CD30 ligand) on normal naive B cells. Signals emanating from B cell CD153 interfere with the CD154-induced recruitment of TNF receptor-associated-protein (TRAF)2, TRAF2, TRAF3, TRAF5, TRAF6 and TNF-associated activator of NF-kappaB (**TANK**) to CD40. They also inhibit the CD154-induced activation of IkappaB kinase (**IKK**), the degradation of IkappaB, and the subsequent nuclear translocation of NF-kappaB, a transcription factor critical for CSR to occur. By showing that engagement of T cell CD30 by CD153 on leukemic B cells down-regulates CD154, our findings suggest that, in CLL, dysregulated CD30:CD153 interaction impairs class switching and antibody production by transmitting bidirectional CD40 and CD154-inhibitory signals.

L49 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 7  
 AB BACKGROUND: NF-kappaB is an ubiquitously expressed transcription factor that plays an important role in the immune, anti-apoptotic and inflammatory responses. NF-kappaB is normally sequestered in the cytoplasm by interacting with inhibitory IkappaB molecules. Upon stimulation, IkappaB is phosphorylated and subsequently degraded by the proteasome, allowing NF-kappaB to translocate into the nucleus where they regulate target gene expression. Two kinases, **IKK**-alpha and **IKK**-beta, which are responsible for IkappaB phosphorylation were recently identified. We have recently identified a cytokine inducible **IKK**-i, a kinase related to **IKK**-alpha and -beta. **IKK**-i significantly induced NF-kappaB activation upon over-expression, as did **IKK**-alpha and **IKK**-beta. Unlike **IKK**-alpha and **IKK**-beta, **IKK**-i phosphorylated Ser36 but not Ser32 in vitro, suggesting that **IKK**-i activates NF-kappaB by distinct mechanisms from the conventional **IKKs**. RESULTS: I-TRAF/**TANK** was isolated as a molecule that interacts specifically with inducible IkappaB kinase (**IKK**-i) by the yeast two-hybrid screening procedure. The association of **IKK**-i and I-TRAF is mediated via the interaction between the N-terminal domain of I-TRAF and the C-terminal portion of **IKK**-i. In vitro kinase assays demonstrate that **IKK**-i phosphorylates I-TRAF in the middle portion that associates with TRAF2. Interestingly, TRAF2 is freed from the I-TRAF/TRAF2 complex after I-TRAF phosphorylation. NF-kappaB activation by **IKK**-i is significantly blocked by coexpression of the N-terminal domain of I-TRAF, dominant negative TRAF2, and dominant negative NIK and **IKK**-beta. **IKK**-i over-expression also induced c-Jun N-terminal kinase. These results show that I-TRAF is a substrate of **IKK**-i. NF-kappaB activation by **IKK**-i may be mediated through phosphorylation of I-TRAF by **IKK**-i and subsequent liberation of TRAF2. CONCLUSION: These results indicate that NF-kappaB activation by **IKK**-i is mediated through phosphorylation of I-TRAF/**TANK** by **IKK**-i and subsequent liberation of TRAF2.

L49 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 8  
 AB The activation of NF-kappaB by receptors in the tumor necrosis factor (TNF) receptor and Toll/interleukin-1 (IL-1) receptor families requires the TRAF family of adaptor proteins. Receptor oligomerization causes the recruitment of TRAFs to the receptor complex, followed by the activation of a kinase cascade that results in the phosphorylation of IkappaB. **TANK** is a TRAF-binding protein that can inhibit the binding of TRAFs to receptor tails and can also inhibit NF-kappaB activation by these receptors. However, **TANK** also displays the ability to stimulate TRAF-mediated NF-kappaB activation. In this report, we investigate the mechanism of the stimulatory activity of **TANK**. We find that **TANK** interacts with TBK1 (**TANK**-binding kinase 1), a novel **IKK**-related kinase that can activate NF-kappaB in a kinase-dependent manner. TBK1, **TANK** and TRAF2 can form a

ternary complex, and complex formation appears to be required for TBK1 activity. Kinase-inactive TBK1 inhibits **TANK**-mediated NF-kappaB activation but does not block the activation mediated by TNF-alpha, IL-1 or CD40. The TBK1-**TANK**-TRAF2 signaling complex functions upstream of NIK and the **IKK** complex and represents an alternative to the receptor signaling complex for TRAF-mediated activation of NF-kappaB.

=> s l12 and (nfkb or nf(w)kappa(w)b or nf(w)kb)

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35618 KAPPA  
553586 B  
12197 NF(W)KAPPA(W)B  
20871 NF  
49123 KB  
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FILE 'SCISEARCH'

329 NFKB  
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55899 KAPPA  
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21124 NF(W)KAPPA(W)B  
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41327 KB  
1436 NF(W)KB

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1904 NF  
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L62 6 DUP REM L61 (0 DUPLICATES REMOVED)

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L62 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Modified receptors on cell membranes for the discovery of therapeutic ligands

SO PCT Int. Appl., 122 pp.

CODEN: PIXXD2

IN Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus

AN 2003:532691 HCAPLUS

DN 139:95435

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055914	A2	20030710	WO 2002-DK900	20021220
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

L62 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Activation of the **Rap** GTPases in B lymphocytes modulates B cell antigen receptor-induced activation of Akt but has no effect on MAPK activation

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (24 OCT 2003) Vol. 278, No. 43, pp. 41756-41767.

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.

ISSN: 0021-9258.

AU Christian S L; Lee R L; McLeod S J; Burgess A E; Li A H Y; Dang-Lawson M; Lin K B L; Gold M R (Reprint)

AN 2003:915407 SCISEARCH

L62 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

TI Use of phosphorylation site-specific antibodies in method for quantifying protein kinase activity

SO PCT Int. Appl., 40 pp.

CODEN: PIXXD2

IN Reagan, Kevin J.; Schaeffer, Erik; Wang, Jimin

AN 2002:256503 HCAPLUS

DN 136:291007

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002027017	A2	20020404	WO 2001-US30186	20010927
WO 2002027017	A3	20030116		
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 2003162230	A1	20030828	US 2001-948972	20010907

EP 1328812                    A2    20030723                    EP 2001-973567    20010927  
 R:    AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
       IE, FI, CY, TR

L62 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI Endocrine disruptor screening using DNA chips of endocrine  
    disruptor-responsive genes  
 SO Jpn. Kokai Tokkyo Koho, 386 pp.  
    CODEN: JKXXAF  
 IN Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto,  
    Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin  
 AN 2002:937303 HCAPLUS  
 DN 138:20443

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	JP 2002355079	A2	20021210	JP 2002-69354	20020313

L62 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI Methods for treatment of human Huntington's disease and methods of  
    screening for active agents  
 SO PCT Int. Appl., 46 pp.  
    CODEN: PIXXD2  
 IN Olson, James M.; Luthi-Carter, Ruth; Young, Anne; Strand, Andrew  
 AN 2001:360024 HCAPLUS  
 DN 134:361383

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	WO 2001034633	A2	20010517	WO 2000-US30900	20001110
	WO 2001034633	A3	20020110		
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	AU 2001017602	A5	20010606	AU 2001-17602	20001110

L62 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN  
 TI Analysis and comparison of partial sequences of clones from a taste-bud  
    enriched cDNA library  
 SO Journal of Dental Research (1997), 76(4), 831-838  
    CODEN: JDREAF; ISSN: 0022-0345  
 AU Hoon, M. A.; Ryba, N. J. P.  
 AN 1997:304880 HCAPLUS  
 DN 127:1555

=> d ab tot

L62 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN  
 AB A drug discovery method is provided for selecting a compound selected from  
    the group consisting of a small organic substance, a biopharmaceutical, or an  
    antibody or part thereof. The method comprises the steps of (i)  
    expressing one or more receptors on a cell membrane, such as, e.g., an  
    exterior cell surface of a cell, (ii) contacting one or more expressed  
    receptors with a test compound or a selection of test compds. (libraries),  
    and (iii) selecting one or more compds. based on its ability to bind one  
    or more receptors. The step of expressing the one or more receptors  
    comprises capturing one or more receptors on the exterior cell surface in  
    a conformation that predominantly enables binding or interaction with a  
    ligand, and the conformation that predominantly enables binding or  
    interaction with a ligand is provided by modification of one or more  
    receptors by a method comprising at least one of the following: (a) fusion  
    with any protein which keeps the receptor in the desired conformation such  
    as, e.g. an arrestin, a modified arrestin, a G-protein or a modified  
    G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors  
    may be captured on the exterior cell surface by at least one of the

following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L62 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AB Signaling by the B cell antigen receptor (BCR) activates the **Rap1** and **Rap2** GTPases, putative antagonists of Ras-mediated signaling. Because Ras can activate the Raf-1/ERK pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, we asked 'whether **Rap** activation limits the ability of the BCR to signal via these pathways. To do this, we blocked the activation of endogenous **Rap1** and **Rap2** by expressing the **Rap**-specific **GTPase -activating protein** RapGAPII. Preventing **Rap** activation had no effect on BCR-induced activation of ERK. In contrast, BCR-induced phosphorylation of Akt on critical activating sites was increased 2- to 3-fold when **Rap** activation was blocked. Preventing **Rap** activation also increased the ability of the BCR to stimulate Akt-dependent phosphorylation of the FKHR transcription factor on negative regulatory sites and decreased the levels of p27(Kip1), a pro-apoptotic factor whose transcription is enhanced by FKHR. Moreover, preventing **Rap** activation reduced BCR-induced cell death in the WEHI-231 B cell line. Thus activation of endogenous **Rap** by the BCR limits BCR-induced activation of the PI3K/Akt pathway, opposes the subsequent inhibition of the FKHR/p27(Kip1) pro-apoptotic module, and enhances BCR-induced cell death. Consistent with the idea that **Rap**-GTP is a negative regulator of the PI3K/Akt pathway, expressing constitutively active **Rap2** (Rap2V12) reduced BCR-induced phosphorylation of Akt and FKHR. Finally, our finding that Rap2V12 can bind PI3K and inhibit its activity in a manner that depends upon BCR engagement provides a potential mechanism by which **Rap**-GTP limits activation of the PI3K/Akt pathway, a central regulator of B cell growth and survival.

L62 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

AB The invention involves a method for measuring phosphorylation of proteins and, as such, is an indicator of protein kinase activity. The method involves the in vitro phosphorylation of a target protein but subjecting that protein (non-phosphorylated) to reaction mixture containing all reagents, including phosphokinase which allow the creation of a phosphorylated form of protein. The phosphorylated protein is measured by contacting it with an antibody specific for the phosphorylation sites(s). The invention includes antibodies useful in practicing the methods of the invention. The invention particularly relates to phosphorylation of Tau, Rb and EGFR proteins and antibodies specific for the site of phosphorylation of the Tau, Rb or EGFR proteins.

L62 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17- $\beta$  estradiol (E2), were found in mice by DNA chip anal.

L62 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

AB Genes modulated by the expression of a mutant huntington protein associated with Huntington's Disease have been determined. A profile of mRNAs that are modulated has been established as neurodegeneration progresses through the disease. Levels of mRNA encoding components of neurotransmitters, calcium and retinoid signaling pathways at both early and late symptomatic disease states have been established. Methods for the treatment or amelioration of disease have been determined based on the mRNA profile determined. Further, methods for screening for agents active in ameliorating and/or preventing progression of Huntington's Disease can be determined by examining changes in the level of expression of the mRNAs and/or proteins of the Huntington's Disease profile of the present invention.

L62 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN

AB Differential patterns of cellular development and function are determined, at least in part, by the specific gene expression of particular cells. Thus, determination of differential patterns of gene expression between tissues is likely to help elucidate mol. details of tissue-specific processes. Our hypothesis was that cells of the circumvallate papilla involved in taste perception would express genes that are not expressed in the surrounding epithelium and that determination of the nature of these genes could be helpful in our understanding of the mol. details of taste. Using partial sequencing of clones derived from rat circumvallate papillae, we have begun to characterize genes that could be important in taste. We prepared a cDNA library of whole circumvallate papillae and, by means of a novel subtraction procedure, enriched taste-specific clones. Characterization of the libraries showed that subtraction resulted in good enrichment of taste-specific clones. Here we report the partial sequencing and anal. of 410 cDNA clones from the taste-bud-enriched cDNA library. Approx. 25% of the genes were identified on the basis of their high homol. to known transcripts. These included the developmentally important mols. Pax-1, espl, Notch 1, and Notch 3 that may play roles in the continuous turnover of taste receptor cells. A further 20% of the genes had not significant homol. to known DNA sequences and were identified as taste-specific by Southern blot anal.

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